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Physical function, physical activity and quality of life in systemic sclerosis

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To all patients with SSc with the hope that this Thesis will spread some new knowledge, insights and, maybe, help.

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ABSTRACT

Background and aims: Systemic sclerosis (SSc) is a multisystem rheumatic disease characterized by fibrosis, vasculopathy and immune system activation. There is a dearth of knowledge how different subphenotypes such as patients with no–mild and moderate–end-stage lung disease differs in physical function and activity, muscle function and active range of motion. Likewise, no study has yet investigated what experiences patients with SSc have of physical activity and exercise. Although it is known that many patients with SSc have physical disabilities, reduced health-related quality of life (HRQoL) and have anxiety and depression symptoms, little is known about differences between patients with no–mild and moderate–end-stage lung disease respectively. The overarching aim of this Thesis was to increase the knowledge of physical function, physical activity and HRQoL in patients with SSc and different degrees of lung disease. The specific aims were to investigate the differences in physical capacity, physical activity, muscle function and range of motion in comparison with population-based controls or reference values. Further, a specific aim was to explore patients' own experiences of physical activity and exercise.

Participants and methods: Three Cross-sectional studies were performed. In paper 1, 106 patients with SSc and 106 age- and gender-matched population-based controls were involved. In paper II, 205 patients with SSc were compared with reference values and in a paper III, 279 patients were involved. Further, a qualitative study with interviews of 16 individuals with SSc were performed and underwent a content analysis.

Results: ***Paper I:*** Patients with SSc reported overall lower physical capacity for walking, jogging, and running, and more limiting factors for physical capacity than controls. Patients with no–mild lung disease reported pain more often than their controls, whereas moderate–severe lung disease patients reported cardiopulmonary disease and reduced muscle strength as limiting factors for physical capacity more often than their controls. More patients than controls had 'never exercised' for at least 30 min per occasion within the past year; however, there were no differences overall between patients and controls in frequency of exercise, physical activity, nor time spent sitting. ***Paper II:*** Shoulder- and hip flexion muscle endurance were lower in relation to reference values, median [53% and 40% of predicted], respectively. Patients with moderate–end-stage lung disease had lower endurance in shoulder- and hip flexion [39% and 35%] than patients with no-mild lung disease [57% and 48%]. All patients, regardless subtype/grouping, needed longer time to complete the Timed-Stands Test (TST) [21 s] compared to reference values [17 s], and patients with moderate–end-stage lung disease needed longer time to complete TST than patients with no-mild lung involvement, [25 s vs 19 s]. Active range of motion in shoulder-arm were lower compared with reference values,

and patients with dcSSc had lower shoulder-arm movement than patients with lcSSc. ***Paper III:*** The following three themes (and categories) emerged from the analysis: Essential for life and health (Diminishes symptoms and is as effective as pharmaceuticals, Reduces fear of deterioration, and, Feeling healthy and satisfied with oneself); Disease-related and other hindrances (Breathlessness, pain and other disease consequences limit, Risk of worsening, and, Non-disease barriers); and, Own understanding about physical activity/exercise and support from healthcare (Experience-based knowledge about own capability and physical activity/exercise, and, Education and support from healthcare and others). ***Paper IV:*** Patients with moderate–end-stage lung disease scored lower on Medical Outcomes Trust Short Form 36 (SF-36) physical component score than no–mild. Patients with moderate–end-stage lung disease had lower physical capacity, were less physical active on low-moderate intensity and exercised less the past year compared with no–mild. Patients with moderate–end-stage lung disease scored higher on Health Assessment Questionnaire (HAQ) and higher scores on Hospital Anxiety Depression scale (HADs), than the no–mild group. In the whole SSc sample, the SF-36 physical component score correlated highly with HAQ and moderately with symptoms on HAQ-VAS- general, dyspnoea, pain; and physical capacity, while SF-36 mental component score correlated moderately with anxiety and depression (HAD).

Conclusions: Although SSc patients reported lower physical capacity and more limiting factors for physical capacity than controls, there were no differences in reported physical activity and time spent sitting. However, SSc patients have markedly reduced muscle endurance in both the upper and lower extremities, reduced muscle strength in the lower extremities and impaired active range of motion in the shoulders and arms. Patients with moderate-end stage lung involvement had more impaired muscle endurance and strength than those with no-mild lung involvement but surprisingly no differences were found between lcSSc and dcSSc patients. Among individuals with SSc with both no-mild and moderate–end-stage lung disease, physical activity and exercise was expressed as essential for life and health and that it reduces fear of deterioration. Nevertheless, it was also expressed as a risk for worsening. As patients with SSc with moderate-severe lung disease have lower physical capacity, are less physically active and exercise less, are more physically disabled, have a lower physical HRQoL and have more depressive symptoms than patients with no-mild lung disease, individualized physical activity and exercise support from physiotherapist might be beneficial. The studies included in this thesis contributes to new knowledge, about how to develop and evaluate future physical exercise programs including resistance training for patients with SSc, especially for those with more severe lung disease.

SVENSK SAMMANFATTNING

Bakgrund och syften: Systemisk skleros (SSc) är en reumatisk multisystemsjukdom som karaktäriseras av fibros, vaskulopati och immunsystemsaktivering. Det råder brist på kunskap hur olika subtyper, som patienter med ingen–mild och måttlig–mycket svår lungsjukdom, skiljer sig i fysisk kapacitet och fysisk aktivitet, muskelfunktion och aktivt rörelseomfång. Dessutom finns ingen studie som undersökt vilka erfarenheter patienter med SSc har av fysisk aktivitet och träning. Även om det är känt att patienter med SSc har fysiska funktionsnedsättningar, nedsatt hälsorelaterad livskvalitet (HRQoL) och problem med ångest och depression, är lite känt om eventuella skillnader mellan patienter med ingen–mild och måttlig–mycket svår lungsjukdom. Det övergripande syftet med denna avhandling var att öka kunskapen om fysisk funktion, fysisk aktivitet och HRQoL hos patienter med SSc och olika grad av lungsjukdom. De specifika syftena var att undersöka skillnader i fysisk kapacitet, fysisk aktivitet, muskelfunktion och rörelseomfång i jämförelse med befolkningsbaserade kontroller eller referensvärden. Ytterligare ett specifikt mål var att utforska patienternas egna erfarenheter av fysisk aktivitet och träning.

Deltagare och metoder: Tre tvärsnittsstudier utfördes. I delarbete 1 inkluderades 106 patienter med SSc och 106 ålders- och könsmatchade kontrollpersoner. I delarbete II jämfördes 205 patienter med SSc med referensvärden och i delarbete III var 279 patienter inkluderade. Vidare utfördes en kvalitativ studie med individuella intervjuer av 16 personer med SSc där intervjuerna genomgick en innehållsanalys.

Resultat: Delarbete I: Patienter med SSc rapporterade överlag en lägre fysisk förmåga att gå, jogga och springa, och fler begränsande faktorer för fysisk kapacitet än kontrollpersonerna. Patienter med ingen–mild lungsjukdom rapporterade smärta oftare än deras kontroller, medan patienter med måttlig–svår lungsjukdom rapporterade hjärt-kärlsjukdomar och minskad muskelstyrka som begränsande faktorer för fysisk kapacitet oftare än deras kontroller. Fler patienter än kontroller hade ”aldrig tränat” i minst 30 minuter per tillfälle under det senaste året. Det fanns emellertid inga skillnader mellan patienterna och kontrollerna avseende frekvensen av träning, fysisk aktivitet eller stillasittande under dagen. **Delarbete II:** Muskeluthålligheten i axel- och höftflexion var lägre än referensvärden, median [53% respektive 40% av förväntade]. Patienter med måttlig–mycket svår lungsjukdom hade lägre uthållighet i axel- och höftflektion [39% och 35%] än patienter med ingen–mild lungsjukdom [57% och 48%]. Alla patienter, oavsett subtyp/gruppering, behövde längre tid för att slutföra Timed-Stands Test [21 s] jämfört med referensvärden [17 s], och patienter med måttlig–mycket svår lungsjukdom behövde längre tid för att slutföra testet än patienter med ingen–mild lungsjukdom [25 s vs 19 s]. Aktivt rörelseomfång i skuldra-arm var mindre jämfört

med referensvärden, och patienter med dcSSc hade mindre skuldra-armrörlighet än patienter med lcSSc. **Delarbete III:** Följande tre teman (och kategorier) framkom av analysen om fysisk aktivitet och träning: Viktigt för liv och hälsa (Minskar symtomen och är lika effektiv som läkemedel, Minskar rädsla för försämring, och, Känner sig frisk och nöjd med sig själv); Sjukdomsrelaterade och andra hinder (Andfåddhet, smärta och andra sjukdomskonsekvenser begränsar, Risk för försämring, och, Icke-sjukdomsrelaterade hinder); och Egen förståelse för fysisk aktivitet/träning och stöd från vården (Erfarenhetsbaserad kunskap om egen förmåga och fysisk aktivitet/träning, och, Information och stöd från vården och andra). **Delarbete IV:** Patienter med måttlig–mycket svår lungsjukdom hade lägre värden på SF-36 PCS än de med ingen–mild lungsjukdom. Patienter med måttlig–mycket svår lungsjukdom hade lägre fysisk kapacitet, var mindre fysiskt aktiva på låg–måttlig intensitet samt hade tränat mindre det senaste året jämfört med patienter med ingen–mild lungsjukdom. Patienter med måttlig–mycket svår lungsjukdom hade sämre resultat på Funktionsskattningsformuläret (HAQ) och högre poäng på Hospital Anxiety Depression Scale (HAD) än de med ingen–mild lungsjukdom. I hela gruppen korrelerade SF-36 PCS högt med HAQ och måttligt med symtom på HAQ-VAS-allmänt, dyspné, smärta och fysisk kapacitet, medan SF-36 MCS korrelerade måttligt med ångest och depression (HAD).

Slutsatser: Även om patienter med SSc rapporterade lägre fysisk kapacitet och mer begränsande faktorer för fysisk kapacitet än kontroller, fanns inga skillnader i rapporterad fysisk aktivitet och stillasittande under dagen. Patienter med SSc hade emellertid markant lägre muskeluthållighet i både övre och nedre extremiteter, minskad muskelstyrka i nedre extremiteterna och nedsatt skulder-armrörlighet. Patienter med måttlig–mycket svår lungsjukdom hade lägre muskeluthållighet och mindre styrka än de med ingen–mild lungsjukdom, men överraskande fanns inga skillnader mellan lcSSc och dcSSc. Bland personer med SSc med ingen–mild, och måttlig–mycket svår lungsjukdom, uttrycktes det att fysisk aktivitet och träning var nödvändigt för liv och hälsa, och att det minskade rädslan för försämring. Dock uttrycktes det även att det fanns en risk för negativa konsekvenser av fysisk aktivitet och träning. Eftersom patienter med SSc med måttlig–mycket svår lungsjukdom hade lägre fysisk kapacitet, var mindre fysiskt aktiva samt tränade mindre, hade mer fysiska funktionshinder, hade lägre fysisk HRQoL och mer depressiva symtom än patienter med ingen–mild lungsjukdom, kan individanpassad fysisk aktivitet och träning vara av nytta. Delarbetena som ingår i denna avhandling bidrar till ny kunskap om hur man kan utveckla framtida träningsprogram, inklusive uthållighetsträning för patienter med SSc, speciellt för de med svårare lungsjukdom.

LIST OF SCIENTIFIC PAPERS

I. **H Pettersson**, A Åkerström, A Nordin, E Svenungsson, H Alexanderson, C Boström. Self-reported physical capacity and activity in patients with systemic sclerosis and matched controls. Scandinavian Journal of Rheumatology, 2017, Nov;46(6):490-495

II. **H Pettersson**, C Boström, F Bringby, R Walle-Hansen, LTH Jacobsson, E Svenungsson, A Nordin, H Alexanderson. Muscle endurance, strength, and active range of motion in patients with different subphenotypes in systemic sclerosis: a cross-sectional cohort study. Scandinavian Journal of Rheumatology, 2018, Aug 2:1-8

III. **H Pettersson**, A Nordin, E Svenungsson, H Alexanderson, C Boström. Experiences of physical activity and exercise in individuals with systemic sclerosis – a qualitative study. Submitted manuscript.

IV. **H Pettersson**, C Boström, E Svenungsson, H Alexanderson, A Nordin. Health-related quality of life in patients with systemic sclerosis with different degree of lung diseases. A cross-sectional study. Manuscript.

RELATED PUBLICATIONS NOT INCLUDED IN THE THESIS

de Oliveira NC, Portes LA, **Pettersson H**, Alexanderson H, Bostrom C. Aerobic and resistance exercise in systemic sclerosis: State of the art. Musculoskeletal Care 2017;15:316-23.

LIST OF ABBREVIATIONS

ADL	activities of daily living
AROM	active range of motion
COPD	chronic obstructive pulmonary disease
DLCO	diffusing capacity of the lung for carbon monoxide
DU	digital ulcers
dcSSc	diffuse cutaneous systemic sclerosis
FI-2	Functional Index 2
FSA	Functional Shoulder Assessment
FVC	forced vital capacity
GI	gastrointestinal tract
HAD	Hospital Anxiety Depression scale
HAQ-DI	Health Assessment Questionnaire Disability Index
HRQoL	health-related quality of life
ILD	interstitial lung disease
lcSSc	limited cutaneous systemic sclerosis
MCP	metacarpophalangeal
MCS	mental component score in SF-36
mRSS	modified Rodnan skin score
PA	physical activity
PAH	pulmonary arterial hypertension
PAQ	Physical Activity Questionnaire
PCS	Physical component score in SF-36
PFT	pulmonary function test
RA	rheumatoid arthritis
RP	Raynaud´s phenomenon
SSc	systemic sclerosis
SF-36	Medical Outcomes Trust Short Form 36
TST	Timed-Stands Test
VAS	Visual analogue scale

CONTENTS

1 INTRODUCTION

1.1 Systemic sclerosis

Systemic sclerosis (SSc) is a rare autoimmune systemic disease characterised by vasculopathy, fibrosis and autoimmunity [1,2]. The American Rheumatism Association published the first classification criteria for SSc in 1980 [3]. The criteria were revised and updated by the 2013 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) [4], (Table 1). The classification criteria include the skin, lesions, abnormalities in blood vessels, cardiopulmonary manifestations like pulmonary arterial hypertension (PAH) and lung fibrosis/interstitial lung disease (ILD). A total score is calculated through adding the maximum score in each of the eight sub-items. Patients with total score ≥9 are considered to have definite SSc. Tight skin on fingers on both hands extending proximal to the metacarpophalangeal (MCP) joints is considered as a sole criterion for SSc. Based on the extent and location of skin involvement SSc is traditionally grouped into two distinctive subtypes; limited cutaneous SSc (lcSSc) and diffuse cutaneous SSc (dcSSc) [5-7]. In patients with lcSSc skin tightness is limited to parts distal to elbows or knees, whereas those with dcSSc have more widespread skin changes affecting proximal limbs and/or trunk. Face involvement can be present in both subtypes [6,7]. This clinical classification can be considered as a help to classify patients according to presence and extent of skin involvement, and also to predict future internal organ disease and survival [6].

Raynaud's phenomenon (RP) is together with involvement of the gastrointestinal tract (GI) the first symptoms of SSc and they are almost universal in both subtypes of the disease [6].

Recent research highlights the importance of investigating the presence of antinuclear antibodies (ANA) in patients with SSc, since the autoantibody pattern helps to improve diagnosis and identification of disease subsets as wells as to improve patient's care and management [8,9]. Over 90% of patients with SSc display ANA [1,10]. The most common and clinically relevant subsets of ANA in SSc are anti-topoisomerase I antibodies (ATA) and anti-centromere antibodies (ACA) [1,10]. In Caucasian populations ACA is more common than ATA, occurring in up to 90% and 40% respectively [10-12]. The presence of ANA is often present prior symptom onset and titres of ANA are often stable during the course of the disease [6]. The ANA-subgroups are in most cases associated with different clinical patterns of disease.

Table 1. The American College of Rheumatology/European League Against Rheumatism criteria for the classification of systemic sclerosis (SSc) [4].

Item	Sub-item(s)	Score
Skin thickening of the fingers of both hands extending proximal to the MCP joints (sufficient criterion)	-	9
Skin thickening of the fingers (only count the highest score)	Puffy fingers Sclerodactyly of the fingers (distal to the MCP but proximal to the interphalangeal joints)	2 4
Fingertip lesions (only count the highest score)	Digital tip ulcers Fingertip pitting scars	2 3
Telangiectasia	-	2
Abnormal nailfold capillaries	-	2
PAH and/or ILD (maximum score is 2)	PAH ILD	2 2
RP	-	3
SSc-related ANA's (maximum score is 3)	ACA ATA A-RNA III	3 3 3

MCP: metacarpophalangeal; PAH: pulmonary arterial hypertension; ILD: interstitial lung disease; RP: Raynaud´s phenomenon; ANA: anti-nuclear antibodies; ACA: anti-centromere antibodies; ATA: anti-topoisomerase I antibodies; A-RNA III: anti-RNA polymerase III antibodies. The total score is determined by adding the maximum score in each category and a total score ≥9 is considered as having definite SSc.

The incidence and prevalence of SSc varies globally depending on regions and ethnicity. The reported incidence varies between 4–43 per million and the prevalence between 70–340 per million [13]. In a study published 2014 [14], including all residents in Skåne, the southernmost region of Sweden with a population of 1.3 million inhabitants, the adult annual incidence and prevalence of SSc were 14 and 235 per million, respectively. Between 60–80% of the patients worldwide are diagnosed with lcSSc, while approximately 20–40% of patients have dcSSc [2,5]. The Swedish study showed that 82% of the prevalent cases were diagnosed with lcSSc [14]. As in many other rheumatic diseases female gender predominates in patients with SSc with a female/male ratio of 6:1 [1], however the gender ratio differs between the two diagnostic subgroups with a ratio of 11:1 in lcSSc and 4:1 in dcSSc [1].

1.2 Organ manifestations and disease severity

Several different organ systems can be affected in SSc, and the extent of disease damage and disease severity is often assessed by the Medsger disease severity scale [15] which grades nine areas affected by the disease: (1) General, (2) Peripheral Vascular, (3) Skin, (4) joint/tendon, (5) Muscle, (6) Gastrointestinal tract, (7) Lung, (8) Heart and (9) Kidney. The scale measures disease damage between 0, indicating normal function/no impairment or damage, to 4, end-stage. The end-stage score of 4 points means that a patient is dependent of supplemental oxygen if the score 4 occurs in the organ system Lung, and when a 4 is scored in the organ system Heart it means that the patient is suffering from congestive heart failure and has a left ventricular ejection fraction of <30%.

Skin thickness is usually measured by the modified Rodnan skin score (mRSS) [16]. The mRSS is also included in the Medsger disease severity score as part of the organ system Skin [15].

1.3 Fibrosis and vasculopathy

1.3.1 Fibrosis

Fibrosis of the skin is one of the hallmarks of SSc and the term scleroderma, hard skin, is used to describe the hard woody like skin feature [17]. The fibrotic changes do not only affect the skin but also different internal organs such as the GI, the lungs and the heart [6]. Diffuse cutaneous SSc is associated with earlier occurrence of severe lung fibrosis/ILD, cardiac fibrosis and an overall worse prognosis. The ILD is due to thickening of the interstitium caused by autoimmunity and/or inflammatory processes [2,5,18–20].

1.3.2 Vasculopathy

The vascular spasm in RP is episodical, painful, and mainly affects fingers or toes but also the nose and ears. The ischemia is mainly provoked by exposure to cold temperatures, changes in temperatures and/or stress [6,21]. More than 50% of patients have a history of digital ulcers, and approximately 10% of all patients with SSc currently have digital ulcers [22]. The pathophysiology of digital ulcers is multifold, and often vasospasm and vasculopathy (e.g. intimal fibrosis and endothelial dysfunction) are contributing factors [23]. Not only are ulcers very painful, digital ulcers also take a very long time to heal [22]. The most feared and severe form of vasculopathy is PAH [23,24]. Albeit patients with SSc can be affected by all forms of pulmonary hypertension, PAH is the most common type [25]. The vascular disease in the lungs in SSc is characterized by narrowing and occlusion of the pulmonary arteries. The risk factors for developing isolated PAH are long disease duration, presence of ACA and the belonging to the lcSSc subtype [26].

1.4 Cardiopulmonary function in SSc

1.4.1 Consequences of cardiopulmonary symptoms

Lung fibrosis and PAH are two common and serious consequences of the disease, both leading to a decline in lung function [23,27]. They are potentially lethal complications and the most common causes of death in SSc [6,28] with lung fibrosis-related mortality in 19%, isolated PAH in 14% followed by myocardial (overall) causes in 14% [28].

Dyspnoea is a cardinal symptom of both ILD and PAH and indicate a more severe form of disease, however, dyspnoea at exertion can also be a symptom of deconditioning due to inactivity [29]. Regardless of origin, dyspnoea, or shortness of breath/breathlessness is often experienced by patients with SSc [30].

1.4.2 Assessment of cardiopulmonary function

The use of high-resolution computed tomography (HRCT) is a well-established method to assess signs of lung fibrosis/ILD in SSc [6,25,31]. Clinically relevant lung fibrosis is present in approximately 25% patients with SSc [25] but fibrosis/ILD is observed in up to 90% of cases with SSc, if also subclinical lung fibrosis/ILD is included [32].

By use of pulmonary function tests (PFT) the presence, and severity, of fibrosis can be detected [33]. The forced vital capacity (FVC) and diffusing capacity of the lung for carbon monoxide (DLCO) are both important variables. Values ≥80% of predicted FVC and DLCO are considered as normal in individuals without respiratory limitations [25], however, PFT also have certain disadvantages as the normal range of FVC is 80–120%. In cases where patients have an FVC and/or DLCO >80% of predicted values, but present progression of respiratory problems further evaluations are needed [25,32]. The spirometry variable FVC [34] is a useful measure to predict prognosis and mortality in patients with lung fibrosis [26]. The risk factors for developing severe ILD are early dcSSc and ATA, especially in patients that have a reduction in FVC during the first 18 months since disease onset. Unlike idiopathic ILD the decline in FVC may stabilize around 60–70% of predicted values for many years [26]. Pulmonary function tests assessing DLCO [35] and transthoracic echocardiography are recommended as to screen all patients with SSc for PAH [36].

1.4.2.1 Lung disease severity scale

The Medsger Disease Severity scale combines findings from PFT (DLCO and FVC) with the classification of (no)/presence of fibrosis on HRCT and elevated pulmonary arterial pressure to assess lung disease severity in SSc [15] (Table 2). Each measure is scored using the most severe of the included values in the scoring. In this Thesis patients with a score of 0–1 on the Medsger scale were classified as having no–mild lung disease and those with 2–4 as having moderate–end-stage lung disease.

Table 2. Disease severity of the lungs, according to the Medsger scale [15].

Organ system	0 (normal)	1 (mild)	2 (moderate)	3 (severe)	4 (end-stage)
7. Lung	DLCO ≥ 80%, FVC ≥ 80%, No fibrosis on radiograph, sPAP <35 mmHg	DLCO 70–79%, FVC 70–79%, basilar rales, Fibrosis on radiograph, sPAP 35–49 mmHg	DLCO 50–69%, FVC 50–69%, sPAP 50–64 mmHg	DLCO <50%, FVC <50%, sPAP 65+ mmHg	Oxygen required

DLCO: diffusing capacity for carbon monoxide, % of predicted; FVC: forced vital capacity, % of predicted; sPAP: estimated pulmonary arterial pressure by Doppler transthoracic echocardiography.

1.5 Range of motion

1.5.1 Tight skin

The skin changes in SSc may present in three phases where the initial phase is an inflammatory and oedematous stage where the fingers and hands appear puffy and swollen. In the second and longer phase various degree of sclerotic progressive skin fibrosis occur, typically starting distal to the MCP joints. During this phase contractures in fingers and hands start. In the third phase, skin is gradually becoming softer and atrophic. The skin may return to a state of clinical normality, especially on the upper extremities and the trunk [6,37]. The tight skin may restrict active range of motion (AROM) in both upper and lower extremities [38,39]. Tight skin around the mouth can appear in both subtypes, and the characteristic microstomia which limits mouth opening is present in about 70% patients [40]. Excess fibrotic tissue makes the skin hard and can impact facial mimicry and make oral care problematic [37]. Subcutaneous fat can also dwindle or disappear in both the face as well as the hands and feet [6,7]. The changes in appearance is problematic, especially among women [37].

1.5.2 Joints

Progressive skin thickening/changes can give rise to contractures affecting mainly the fingers/hands in SSc. Joint involvement, both presented as generalized arthralgia with stiffness and slight pain as well as inflammatory arthritis, eventually affects between 46–97% of all patients with SSc [41]. These alterations can cause reductions in grip strength and impaired dexterity [6,38]. Joint contractures affect about 1/3 and causes functional disability due to skin sclerosis, tendon shortening and/or joint destruction [42]. Several studies have shown that patients with dcSSc, but also lcSSc, are affected by severe AROM impairments [43–45]. In addition, contractures (reductions in ROM <75% of normal values), are very common in wrists and hands affecting more than 75% of patients with SSc. Larger joints like

the shoulders are affected in 50% in flexion-extension, abduction-adduction in 15% while contractures are found to a lesser extent in the lower extremities, in approximately 10% in hip, knee and ankle [44,46]. Limited AROM in the lower extremities has also been found in SSc, especially in dcSSc [39,47]. Yet, there is limited insight on the impact of lcSSc/dcSSc to what extent functional AROM in activities of daily living (ADL) is affected in the shoulder-arm region and whether this influence the possibilities to be physically active (PA) and exercise.

1.6 Muscle strength and muscle endurance

Muscle involvement in SSc varies widely but is reported to be present in between 5–96% of patients [48] and is more common in dcSSc than in lcSSc [1,48].The big diversity in reported frequency is mainly due to different methods when assessing muscle involvement and also lack of consistently accepted definition of myopathy [48]. Proximal muscle weakness in shoulder and hip-pelvic region is a prominent symptom in SSc [6,49]. Functional strength, as in standing up from a sitting position, is also reduced in comparison with normative data. Differences between subtypes of SSc are present as patients with lcSSc can perform more sit-to-stand movements than patients with dcSSc. Patients with SSc were more limited in the timed up and go test compared to normative data [39]. Muscle endurance in the quadriceps muscles has also been found to be reduced in comparison with controls [50]. Others have used tests like the Keitel functional test, and the 30-second timed sit-to-stand, that both measures muscle function in the lower extremities [39]. Muscle strength as well as muscle endurance can also be assessed with an isometric dynamometer [50]. Nonetheless, there is a dearth of knowledge about how muscle strength and muscle endurance is affected, especially in patients with different degrees of lung disease, and what consequences muscle impairment has in the lives of patients with SSc.

1.7 Pain and tiredness/fatigue

Pain is a common symptom in patients with SSc [30] with arthralgia and myalgia among the earliest musculoskeletal symptoms [6]. The frequency of self-reported pain has been reported as ~85% in joints, ~75% in muscles as well as ~55% in skin [30]. Pain originating from RP is one of the most frequently reported symptoms in SSc [30,51]. Furthermore, digital ulcers are also very painful [22]. There is a lack of knowledge on how patients with SSc perceive pain in relation to PA/exercise and physical capacity and whether there are any differences in regard to lung involvement. Fatigue is another disease-related symptom affecting many patients with SSc. This overwhelming tiredness is not only very frequent, but also one of the symptoms with highest impact on everyday activities [30]. Severe fatigue is associated with more pain, worse sleep quality and greater depressive symptoms [52].

1.8 Disability

Due to the heterogenous nature of SSc different degree of limitations in function can be encountered. Primarily the hands are affected but also the face is affected by local disability [37]. Among patients with SSc ADL can be a major problem as finger flexion and extension and grip strength has been found to be impaired in comparison with healthy persons [38]. Not only activities involving the upper extremities, like dressing or lifting/holding objects and other household activities, are affected, the lower extremities are also influencing the possibilities to partake in activities. It has been reported that climbing stairs, getting in/out of a car and leisure activities like sports are troublesome [30,53].

Patients with dcSSc have more disabilities compared to patients with lcSSc when assessed with the Health Assessment Questionnaire Disability Index (HAQ-DI) [54,55]. There are little if any correlations between FVC and DLCO and HAQ-DI but a moderate correlation has been presented between dyspnoea and HAQ-DI [56]. Yet no study has evaluated the impact of lung disease, as measured with the Medsger disease severity scale, on disability in SSc.

1.9 Quality of life, anxiety and depression

1.9.1 Health-related quality of life

The World Health Organization defines quality of life as an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad ranging concept affected in a complex way by the person's physical health, psychological state, personal beliefs, social relationships and their relationship to salient features of their environment [57].

The term quality of life is, in the same way as health is, ambiguous and not easily given a distinct definition. Both concepts are reflecting different aspects of well-being, but the quality of life has a considerably broader content. Health-related quality of life (HRQoL) means a pragmatic delimitation, and primarily relates to function and well-being during illness and treatments [58].

Measurements of HRQoL can be done with different self-reported questionnaires, but the generic Medical Outcomes Trust Short Form 36 (SF-36) is probably the most well-known and used tool, in SSc as well as in other populations and samples. The HRQoL, as measured by SF-36, has been found to be lower among patients with SSc compared with the general population, and patients with dcSSc have lower HRQoL than lcSSc [59]. Patients with dcSSc report lower scores on physical and mental aspects of HRQoL compared to patients with lcSSc [60]. Dyspnoea has been found to correlate with HRQoL whereas no correlations were found with objective lung damage in a study with lcSSc without signs of PAH [56]. Another

study reported that patients with SSc with ILD, and patients with chronic obstructive pulmonary disease (COPD) have lower scores in the physical HRQoL in relation to the general population [61]. So far, no study has evaluated the HRQoL in patients with different degrees of lung disease as measured with the Medsger disease severity scale.

1.9.2 Anxiety and depression

Due to the reduced life expectancy in dcSSc, which is associated with internal organ involvement [62] it is understandable that anxiety and depression symptoms are common in SSc [63]. Clinically relevant self-reported anxiety is more frequently reported in women, whereas men are more often free from symptoms of both anxiety and depression when measured with the Hospital Anxiety and Depression scale (HAD) [64]. If levels of anxiety and depression symptoms differ depending on degree of lung involvement as measured with the Medsger score is unknown.

1.10 Physical capacity and activity

In this Thesis we define physical capacity as self-reported ability to walk, jog or run. Physical activity (PA) has been defined as any bodily movement that is produced by skeletal muscles and resulting in an energy expenditure. PA in the daily living can be categorized into household, occupational, conditioning, sports, or other activities. Exercise is a subset of physical activity that is planned, structured, and repetitive and has, as a final or an intermediate objective, the improvement or maintenance of physical fitness. Physical fitness is a set of attributes that are either health- or skill-related [65].

Reduced PA has been observed in patients with early SSc without pulmonary involvement, and nearly ¾ were below recommended levels of PA in comparison to only 27% of age- matched controls [66]. Likewise, in patients with lcSSc and with PAH reduced PA has been reported in comparison with patients without PAH [67]. Self-reported PA has also been found to be significantly lower among patients compared to the general Dutch population [68]. There are yet no publications presenting results whether there are any differences in PA between patients with no–mild and moderate–end-stage lung disease, nor between patients and true age- and gender-matched controls.

Patients with SSc without lung involvement have a significantly lower aerobic capacity compared with healthy controls as measured by maximal exercise test on a treadmill [69]. Likewise did maximal ergometer testing show that patients with PAH had lower maximal oxygen uptake than patients without PAH, but both groups had a clear limitation in exercise performance when compared to predicted values [70]. How self-reported physical capacity is perceived in patients with SSc with different degrees of lung involvement, and if there are any differences between groups, remains unknown.

1.11 Experiences of Physical activity/exercise

In other chronic rheumatic diseases, such as rheumatoid arthritis (RA), PA/exercise have been reported to be perceived as important contributors to symptom management including pain relief and joint function. Both pain and fatigue as well as reduced mobility and stiffness have been reported as barriers to PA/exercise in RA [71]. Similar findings are presented in ankylosing spondylitis (AS) where pain, stiffness and fatigue were the main barriers to PA/exercise while the most often reported benefits of PA/exercise were improved fitness, increased vitality and improved mood [72]. Shortness of breath is experienced as a major barrier for PA/exercise in patients with pulmonary diseases such as COPD, while feeling fit and having better breathing outcomes, and support from others, like health professionals such as physiotherapists, were facilitating factors [73].

However, very little is known about how patients with SSc perceive PA/exercise, and what experiences they have from being PA/exercise, nor what is considered as facilitating and hindrances.

1.12 Pharmacological treatments

There are no curative treatments available for patients with SSc, however, many of the different symptoms can be alleviated by pharmacological drugs [7]. Intensive research is underway, and many patients have already had their disease burden eased by use of immunosuppressive treatments as well as blood vessel modulating treatments [7].

1.13 Non-pharmacological treatments

In the newly revised recommendations for Modern Rheumatological Rehabilitation (MoRR) the aims of rehabilitation in rheumatic diseases are to regain and/or maintain physical function and participation in society [74]. This can be done by prevention, needs-driven individual interventions, team rehabilitation in an outward setting, and after this, in an in-ward setting. Regardless rehabilitation level physiotherapists are key-players as they, as well as PA/exercise, are fundamental in the rehabilitation of patents with rheumatic diseases [74].

Because no curative pharmacological treatments are available for patients with SSc rehabilitation is a possible way to ease the disease burden. However, there is limited knowledge and guidelines about non-pharmacological care in SSc, mainly because of the large variety in studied interventions as well as in the outcomes. Furthermore, the studied samples are in many cases small and/or lacking control groups [37,75]. Our research group, in collaboration with Brazilian researchers, have in a literature review found that physical exercise in patients with SSc with no or mild lung disease has shown positive effects concerning physical capacity,

HRQoL and could be considered safe [76]. However, there are few studies [76] concerning the effects of exercise in patients with SSc with moderate to severe lung disease. But improvements in aerobic capacity [77] and muscle endurance [78] have been reported in patients without ILD after participation in exercise programmes. In a small study in patients with SSc with and without pulmonary involvement, increased muscle strength and aerobic capacity was seen after 12 weeks resistance and aerobic exercises [79]. The aims in hand rehabilitation are to improve both movement and strength in hands, and ameliorate participation in ADL like personal self-care, house-hold activities and leisure activities [37]. Different techniques to treat musculoskeletal impairments have been used with various results [80]. Hand stretching was beneficial [81], as was connective tissue massage [82]. Paraffin wax bath in combination with hand exercise has also been found to improve function more than sole exercise [83].

1.14 Clinical outcome measures in SSC

1.14.1 Range of motion

Goniometer is often used by physiotherapists, as well as occupational therapists, when measuring active and passive ROM, as has been used in previous studies [44,46,84]. Another way to assess AROM in the upper extremities in rheumatic diseases is with the Functional Shoulder Assessment (FSA) [85]. This instrument was originally developed for patients with RA. In the original version of FSA four tasks were assessed [85], but a revised version with five tasks has been developed [86].

1.14.2 Muscle function

Muscle strength, and muscle endurance, can be measured in different ways. An isometric muscle test measures muscle function in a static position, the muscle tries to contract but does not change in length, whereas in an isotonic muscle test the muscle changes in length. Functional muscle strength in the lower extremities can be measured with the Timed-Stands Test (TST) [87]. Another, similar test, is the 30-second timed sit-to-stand, that also measures muscle function in the lower extremities [88]. The Timed Up and Go test can also be used as a physical fitness test for assessing agility/dynamic balance [89].

Muscle strength has often been measured by use of the manual muscle test (MMT), however this instrument is limited by ceiling effects in patients with mild muscle strength weakness [48]. Dynamic repetitive muscle endurance can be measured with Functional Index-2 (FI-2), an instrument originally developed for patients with myositis [90].

1.14.3 Pain and tiredness/fatigue

Pain can be assessed in various ways, either by use of a numeric rating scale [91], visual analogue scale (VAS) [92], or self-reported HRQoL such as in SF-36 [58].

Assessments of fatigue can be done with several different questionnaires [93,94].

1.14.4 Disability

The HAQ instrument is a self-reported questionnaire that has become one of the key instruments used when assessing disability and function in rheumatic musculoskeletal disorders. Included in the HAQ is a disability index (HAQ-DI). The HAQ-DI has been adopted to the context of SSc, Scleroderma HAQ (SHAQ) by having five VAS added [95], otherwise than this both HAQ and SHAQ are scored the same way [96]. The five VAS measures pain, patient general assessment, vascular, digital ulcers, lung involvement and gastrointestinal involvement [95,96].

1.14.5 Health-related quality of life

There are several instruments that are used to assess HRQoL, both generic and diseases/symptom-specific. One generic is the EuroQol instrument, subsequently called EQ-5D [97] and another is the well-known Medical Outcomes Study 36-short form (SF-36) [98]. The St George's Respiratory Questionnaire (SGRQ) was originally developed to assess HRQoL in patients with COPD but it has also been used in patients with idiopathic pulmonary fibrosis [99].

1.14.6 Anxiety and depression

The HAD scale was developed to identify possible and probable cases of both anxiety and depression disorders. The HAD scale consists of seven questions each for the anxiety dimension (HADa) and depression dimension (HADd) [100]. In an attempt to prevent disturbances from physical disorders like insomnia, dizziness, fatigue and headaches, symptoms that were related to anxiety and/or depression were excluded from the scale [100].

1.14.7 Self-reported physical activity/exercise and physical capacity

Self-reported physical activity has often been assessed by the International Physical Activity Questionnaire and there are different versions of the instrument available, and also various forms of administration of the questionnaire; as by telephone interviews or by self-administration [101]. Another self-reported questionnaire is the Physical Activity Questionnaire (PAQ) that has been used in systemic lupus erythematosus (SLE) in Sweden [102,103]. The latter questionnaire also assesses exercise, physical capacity along with time spent sitting during day.

1.15 Qualitative content analysis

Experiences of PA/exercise are preferably explored with qualitative research methods as this approach may facilitate a more in-depth understanding of a group of individuals experiences [104]. By using a qualitative method, it is possible to evaluate and gain a deeper understanding in different perspectives [105]. The inquisitive use of qualitative methods can be used when there is insufficient, or a lack of information about a certain topic like how patients with SSc experience PA/exercise. Content analysis is an often-used method in nursing and healthcare research [106,107]. A face-to-face interview can often last between 30 and 90 minutes. Use of a semi-structured interview guide is recommended as it enhance the topics of interest that will be covered by every informant. About 15–20 individual interviews or three-to-four focus group discussions are often enough, depending on data saturation [108].

2 THESIS RATIONALE

Systemic sclerosis is a major cause of disability and increased morbidity as well as mortality. The large diversity of how the disease presents itself; lcSSc/dcSSc, quick progression or stable disease, damage of varying severity in different organ systems, combined with the rarity makes it challenging to both study the disease, and to adequately treat the patients.

Little is known about how, and if, self-reported levels of physical capacity and PA/exercise differ between patients with no–mild and moderate–end-stage lung disease. Likewise, there is a dearth of knowledge as to what extent muscle function and AROM is affected in different subphenotypes of SSc. Nothing has yet been published about how patients with SSc experience PA/exercise, nor what factors are perceived as facilitating, or as hindrances. However, it is well known that patients with SSc have reduced HRQoL, that they often have disabilities affecting their ADL, and that they suffer from symptoms of both anxiety and depression. But less is known about differences/similarities between patients with no–mild and moderate–end-stage lung disease.

Increased knowledge about physical capacity, levels of PA/exercise on different levels of intensity in addition to further knowledge about how much muscle strength, muscle endurance and AROM is affected in SSc, can help develop exercise programs suitable for patients with different degrees of lung disease. Also, by increased insight into how patients experience PA/exercise and what they perceive as facilitating and/or hindrances can improve patient education and support to those in need. With the aim to optimize health for patients with SSc, PA/exercise is an important, and often neglected, addition to medical treatment. This taken together, can hopefully help to increase HRQoL in patients with SSc.

3 AIMS

The overarching aim of this Thesis was to increase knowledge about physical function, physical activity and quality of life in patients with SSc and different degrees of lung disease.

The aims of the included papers were:

I. To investigate potential differences in self-reported physical capacity and activity between patients and an age- and gender-matched population-based control group, as well as between patients with normal–mild and moderate–severe lung disease and their respective controls.

II. To examine functional dynamic muscle endurance in the shoulder and hip-girdle, functional dynamic muscle strength in the lower extremities, and functional AROM of the shoulder-arm region in patents with SSc.

    We also explored possible differences depending on SSc subphenotypes; i.e. lcSSc versus dcSSc, and presence of mild versus severe lung involvement.

III. To explore and describe experiences of PA/exercise in individuals with SSc.

IV. To explore differences/similarities with focus on HRQoL, disabilities, PA/exercise and physical capacity between patients with no–mild lung disease and moderate–end-stage lung disease.

4 PARTICIPANTS AND METHODS

4.1 Study designs

In the papers included in the Thesis, different research designs were used, see Table 3.

Table 3. Overview of the research designs of the papers included in the Thesis.

Paper	Design	Specific analysis methods [a]
I	Cross-sectional cohort study compared with an age- and gender matched population-based controls	Pearson's x^2 or Fisher's exact test, Mann-Whitney unpaired test, Student's t-test.
II	Cross-sectional cohort study compared with reference values	Pearson's x^2 or Fisher's exact test, Mann-Whitney unpaired test, Wilcoxon signed-ranks test.
III	Interview study using exploratory descriptive qualitative design	Content analysis, inductive approach
IV	Cross-sectional cohort study compared with reference values	Pearson's x^2 or Fisher's exact test, Mann-Whitney unpaired test, independent samples *t*-test, Spearman's correlation coefficient

[a] descriptive statistics were used in all papers in the Thesis.

4.2 Participants, reference values used in the studies, and procedures

All patients with SSc are part of the Karolinska University Hospital's SSc-cohort, which consists of patients living in the greater Stockholm region. Demographic and clinical characteristics are presented in Table 4.

4.2.1 Paper I

A total of 106 adult patients with SSc and 106 age- and gender-matched population-based controls living in the Stockholm County were included. All participants were recruited between 2006 and 2009. The control persons were recruited by use of the national identification number which is coded for gender and date of birth. The gender-matched person with the birth date closest to the respective patient was contacted and asked to participate in the study. If the "first choice" declined participation, the second closest was asked, until control person gave her/his consent. In 65 % of cases the "first choice" accepted and participated in the study. The only exclusion criterion was a diagnosis of SSc. All patients, and controls, answered the PAQ.

Table 4. Demographic and clinical characteristics of patients included in the Thesis.

Characteristics	Paper 1	Paper II	Paper III	Paper IV
Participating patients and controls, n	106+106 controls	205	16	279
Age, years	61±12	60 (52–69)	53 (24–73) †	60 (52–69)
Women, %	84	82	81	83
LcSSc/dcSSc, %	79/21	82/18	75/25	84/16
No–mild/moderate–end-stage lung disease, %	55/45	59/41	50/50	58/42
Disease duration, years	9±9	8 (3–13)	8 (1–38) †	5 (2–11)
Medsger disease severity General, % ‡	na	88/10/1/0/1	na	89/10/1/0/0[6]
Peripheral vascular, % ‡	na	17/61/13/8/1[2]	na	14/62/13/10/1[7]
Skin, % ‡	na	9/81/9/1/0	na	10/83/6/1/0
Gastrointestinal, % ‡	na	30/55/13/1/1[13]	na	28/59/12/1/0[16]
Lung, % ‡	28/26/34/10/2	27/31/29/12/1[6]	19/31/31/6/13	28/30/29/12/1[8]
Heart, % ‡	na	80/14/2/2/2[6]	na	81/14/3/1/1[12]
Kidney, % ‡	na	95/4/9/1/1[3]	na	94/4/0/1/1[8]
Pulmonary hypertension, %	8	6	na	8[1]
Lung fibrosis, %	46	38	na	40[1]
DLCO (% of predicted), %	72±19[5]	na	na	74 (61–86)[10]
FVC (% of predicted), %	8417[8]	na	na	87 (76–98)[12]

Values are presented as mean±(SD), % or median (IQR); †: Median (min-max); ‡: Medsger disease severity score 0/1/2/3/4; DLCO: diffusing capacity of the lung for carbon monoxide; FVC: forced vital capacity

The PAQ instrument covers different self-reported aspects of physical capacity, PA and time spent sitting as well as exercise. The PAQ used in this Thesis have moderate to almost perfect test-retest reliability (weighted kappa coefficients 0.55–0.87) as suggested by Landis and Koch [109] and satisfactory content validity in patients with SLE [103].

As part of this Thesis the test-retest reliability of the PAQ was performed on a subgroup (n=51) of patients with SSc. The test-retest reliability was moderate to substantial. The questions regarding PA on a low-moderate intensity past six months had a weighted kappa: 0.57, 95% CI (0.39–0.81), PA on a high intensity past

6 months: 0.66, 95% CI (0.35–0.96), Physical capacity: 0.58, 95% CI (0.42–0.74), Time spent sitting during the day: 0.74, 95% CI (0.47–1.0), and, Exercise past year: 0.74, 95% CI (0.52–0.96).

4.2.2 Paper II

In this study 205 patients with lcSSc/dcSSc were divided into no–mild and moderate–end-stage lung disease. All patients who had performed physical assessments at the physiotherapy department at the Unit of Rheumatology at Karolinska University Hospital, Solna, between September 2006 and May 2017 were included. The FSA was used to measure AROM in the shoulder-arms, FI-2 assessed dynamic muscle endurance in upper and lower extremities, TST was used to measure functional muscle strength in the lower extremities.

For FSA, reference values from the general Swedish population, in intervals of 10 years, was used. These reference values are presented by Olofsson et. al. [110] and in the present study we had access to their original data. In the Olofsson-study they used an earlier version of FSA which consisted of four tasks. The included tasks are assessed on a 6-point Likert scale (1 point being the worst possible function and 6 points is no impairments in AROM), resulting in a total maximum score of 24 points per shoulder-arm in the 4-task version and 30 points in the 5-task version. Also, in the original FSA, the task Hand-to-neck was scored as 1–7 points, we converted this part to 1–6 points as it is scored this way in the most recent version. In this new version the task hand-to-seat has been added giving a total of 30 points for each shoulder. The comparison of results in the patient group and subjects from the general Swedish population was done by using results previously presented by Olofsson et. al. [110] in intervals of ten years which used the 4-task version of FSA. When comparing different subphenotypes of patients with SSc we used the newer, 5-task version of FSA [86].

The FI-2 is commonly used in clinical settings in Sweden. Seven different muscle groups can be assessed and graded separately. In the Thesis shoulder flexion and hip flexion were assessed. The shoulder flexion was assessed in a sitting position with a 1 kg weight cuff around the wrist. The hip flexion was assessed in a supine position with a straight leg. A pace of 40 beats/minute resulted in a pace of 20 repetitions/minute. The maximal number of repetitions (60 per shoulder and leg) was registered. The results can be presented as counts or percentages of maximal repetitions per task. Preliminary reference values have been collected at Karolinska University Hospital, Solna, Sweden (HA), and at the Oslo University Hospital, Norway (RWH). These reference values are based on age intervals of 10 years from the general population. The comparison of patients' FI-2 results with reference values was done on the right side only, due to 88% of reference values being assessed on the right side.

The FI-2 has been found to have "good" to "excellent" intra-rater, and, inter-rater reliability and it does also have a good construct validity in patients with myositis [90], however the test has not been validated in SSc yet.

For the TST, the time needed to complete ten full stands, without help from the hands, from a sitting position is recorded. Reference values for TST, based on gender- and age-matched healthy subjects, in intervals of 5 years, was used when comparing with patients' assessments. The TST has been validated in several rheumatic and other chronic diseases [111].

4.2.3 Paper III

Sixteen patients strategically identified to represent both lcSSc/dcSSc and no–mild and moderate–end-stage lung disease as well as both sexes, various age, and disease duration were interviewed between August 2017 and February 2018. The individual interviews were performed at a secluded room at Karolinska University Hospital, Solna. Each interview took in average 30–60 minutes.

4.2.4 Paper IV

In this study 279 patients were included between September 2006 and December 2018. To be included in the study the participants had to understand Swedish well enough to be able to fill in at least two of the four questionnaires used. The questionnaires used were SF-36, HAQ-DI including the five SSc-specific VAS, PAQ, and HADa/d.

The generic HRQoL questionnaire SF-36 assesses four physical health domains; Physical Function, Role Physical, Bodily Pain, General Health, and four mental health domains; Vitality, Social Function, Role Emotional, and Mental Health. Each domain is scored separately using an item weighting and additive scale. The summed data are then transformed onto a 0–100-point scale. The higher score, the higher quality of life. The scores can be added into global scores; physical component score (PCS) and mental component score (MCS) [98]. The PCS and MCS are standardized to responses from the general Swedish population and they have a mean score of 50 and a standard deviation of ±10 [112].

The HAQ-DI comprises 20 items that are divided into eight functional domains, each of which has two or three component questions adding up to a total of 20 items. The overall score is calculated by adding the highest item score in each of the eight functional domains and then dividing the sum by eight resulting in a score range between 0–3, where 0 means no disability whereas 3 indicate severe disability. The VAS measures self-reported problems the past week; pain, intestinal, breathing, RP and digital ulcers, and also, overall problems today. The within-patient test-retest has been found to be very good, and the validity is also very high [96].

Both the anxiety and depression dimensions that are part of HAD have seven questions each, and each question is scored between 0–3. The total score in each dimension ranges from 0, no clinical symptoms of anxiety or depression, to 21, maximal clinically significant symptoms. Scores between 0–7 are considered as normal, between 8–10 as borderline, and 11 or more as clinically relevant [100]. The instrument has been used in several studies in SSc, but it has not been specifically tested for reliability or validity in SSc [63].

4.3 Data analysis

P-values <0.05 were considered statistically significant in papers I, II and IV. All analyses were done on version 23.0 and 24.0 of IBM SPSS Statistics for Windows (IBM, Armonk, NY, USA).

4.3.1 Paper I

In **paper I** differences in nominal variables, like gender, reported limiting factors to physical capacity such as poor fitness yes/no, or exercise past year ≥3 times/w, were analysed with Pearson's χ^2 or Fisher's exact test, when appropriate. The significance of differences between groups were either calculated by Mann-Whitney unpaired test or Student's t-test when appropriate for continuous variables.

4.3.2 Paper II

In **paper II** Pearson's χ^2 or Fisher's exact test was used when analysing differences in nominal variables, Mann-Whitney unpaired test was used for ordinal and non-normally distributed continuous variables whereas the Wilcoxon signed-ranks test was used when comparing observed values in the SSc-group with age- and gender-specific reference population values.

4.3.3 Paper III

In **paper III** content analysis as described by Graneheim and Lundman was used [107]. The analysis procedure followed a latent content analysis which made it possible to distil the content of the performed interviews into fewer content-related subcategories and categories. The categories were then grouped into over-arching themes. The latent content explores the *interpreted* meaning in the interview-material.

To get a rich variation of experiences of PA/exercise a purposeful sampling strategy was used [105]. This can help to ensure that a diversity of experiences is gathered in the sample of informants/patients with different degrees of lung involvement, age, gender and mix of lcSSc/dcSSc is included. A broad participation of different degrees of disease severity and other parameters increases the transferability (external validity) of the findings to other patient groups in other settings.

The analysis started by familiarization through re-reading the transcribed interviews while listening to the tape recordings. This process was followed by condensation and coding of meaning units, i.e. constellations of words and sentences belonging to the same central meaning in relation to the aim of the study. In order to increase the credibility of the findings, investigator triangulation was performed with a senior researcher, an co-author of the manuscript, experienced in qualitative research [113]. Grouping and labelling of subcategories and categories were done in an iterative way by frequently returning to the transcripts as well as to the condensations and codes for additional reading to remain in line with the data. The codes were grouped into sub-categories which were then grouped into categories with similar content. The categories were labelled to cover the content of the included subcategories. To further increase the credibility of the analysis the preliminary categories were peer-reviewed in a multi-professional rheumatology healthcare research network group consisting of nurses, occupational therapists and physiotherapists. Main categories were developed by the Author and the senior researcher and discussed with another experienced researcher/co-author [107,114]. The main categories were further developed and sorted into overarching themes and then reviewed by the other researchers involved in the project [107] (Table 5).

Table 5. Steps and actions in the analysis in Paper III.

Steps	Actions
1	**Transcription and familiarization** Verbatim transcription, reading and re-reading to get at good grasp of each interview's content
2	**Condensation of meaning units** Condensation of interviews into meaning units
3	**Coding** Coding of meaning units
4	**Sorting, grouping, and labelling subcategories** Sorting and grouping of codes into subcategories
5	**Organising subcategories into categories** Subcategories combined into preliminary categories
6	**Categories and Themes** Main categories were further merged into three overarching themes

4.3.4 Paper IV

In **paper IV** Pearson's χ^2 or Fisher's exact test was used in the same way as in **paper I and II**, Mann-Whitney unpaired test was used when analysing differences in ordinal or non-normally distributed continuous variables, the independent samples *t*-test was used when analysing results from SF-36 in order to be able to compare with reference values. The Spearman's correlation coefficient (r_s) was used to investigate relationships between SF-36 (PCS and MCS) and other variables. The r_s-values were interpreted as suggested by Munro [115]: $r_s \leq 0.25$ no if any correlation; $r_s = 0.26–0.49$ low; $r_s = 0.50–0.69$ moderate; $r_s = 0.70–0.89$ high; and $r_s = 0.90–1.00$ very high correlation.

4.4 Ethical approval

The research included in the Thesis has been carried out in accordance with the Helsinki Declaration [116]. None of the studies involved any serious medical risks to the patients. The collection of data and publication of results have been carried out to guarantee the integrity and anonymity of the patients. All patients signed written informed consent and were reassured that participation was voluntary and that if they chose not to participate their care at the hospital would not be affected.

All studies included in the Thesis were approved by the Stockholm Regional Ethics Review Board.

Approval numbers: Paper I: dnr 2006/259-31/3. Paper II: dnr 2006/259/31/3 and 2017/591-32. Paper III: dnr 2017/1134-31. Paper IV: dnr 2006/259-31/3 and 2017/591-32.

5 RESULTS

5.1 Paper I: Self-reported physical capacity and activity

Patients with SSc had overall a lower self-reported capacity for walking, jogging, and running than age- and gender-matched population-based controls (Figure 1). The patients also reported more limiting factors for physical capacity ($p<0.001$) than the controls did. Both patients with no–mild lung disease and those with moderate–end-stage lung disease reported lower physical capacity than their respective controls. Patients with moderate–end-stage lung disease reported cardiopulmonary disease ($p<0.001$) and reduced muscle strength ($p=0.03$) more often than their controls, whereas patients with no–mild lung disease reported pain (<0.05) more often than their controls as limiting factors for physical capacity. There were more patients (28%) that "never exercised" for at least 30 minutes/occasion the past year than controls (15%). Among the patients and controls there were no difference in exercise overall the past year or time spent sitting during the day. Likewise, no differences were found in PA past six months overall nor on a high intensity 4–7 days/week, neither were any differences found in PA past six months on a low-moderate intensity.

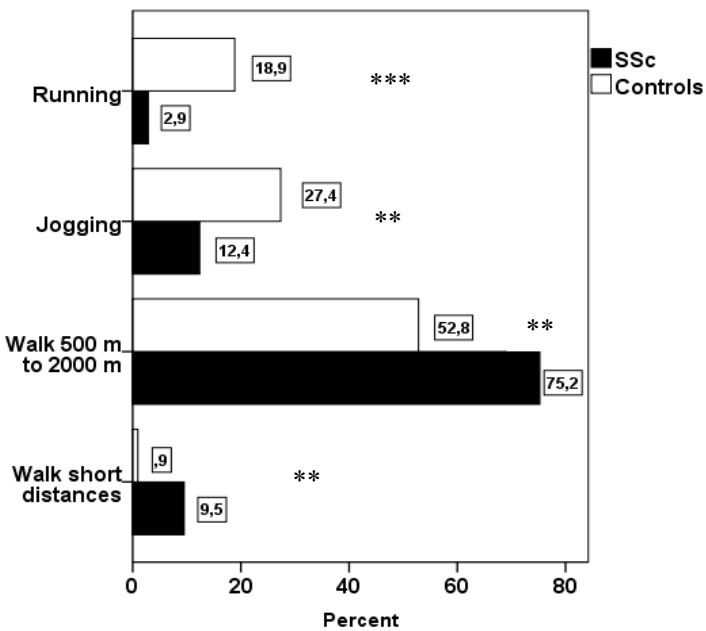

Figure 1. *Self-reported physical capacity in patients with SSc (filled bars) and age- and gender-matched controls. Patients with SSc had overall a lower physical capacity in comparison with the matched population-based control group ($p<0.001$). **$p<0.01$, ***$p<0.001$.*

Patients with no–mild lung disease had overall a lower self-reported physical capacity compared with age- and gender-matched population-based controls (Figure 2A). These patients reported more limiting factor for physical capacity ($p<0.05$), and pain ($p<0.05$) was more often reported as a limiting factor than in their matched controls. No other significant differences were found between the groups.

Patients with moderate–end-stage lung disease did also have an overall lower physical capacity ($p<0.001$) compared with their age- and gender-matched population-based controls (Figure 2B). This subgroup of patients also reported more limiting factor for physical capacity ($p<0.001$), and reduced muscle strength ($p<0.05$) and heart or lung disease ($p<0.001$) were more often found to be a limiting factor than among matched controls. Other than this there were no differences between the groups.

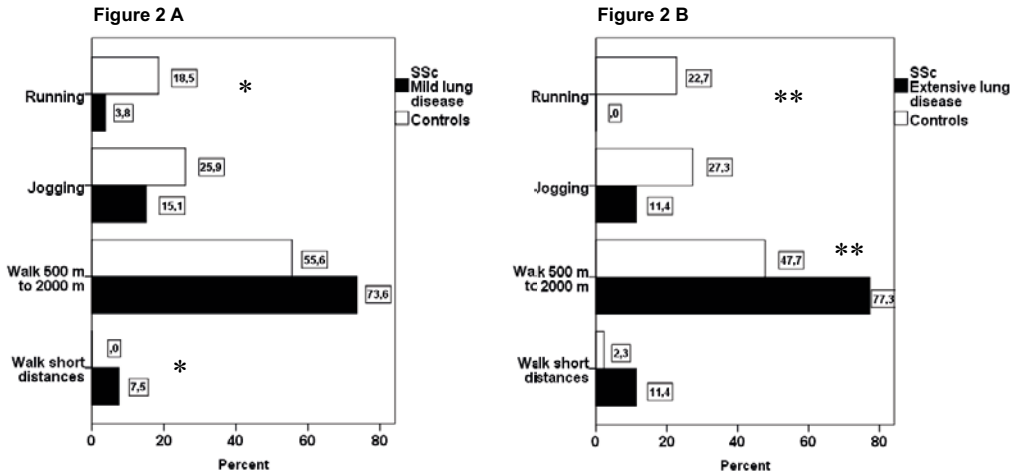

Figure 2 A and B. *Self-reported physical capacity in patients with SSc and no–mild lung disease A, (filled bars) and moderate–end-stage lung disease B, (filled bars) and age- and gender-matched controls.*

(A) Patients with no–mild lung disease had overall a lower physical capacity in comparison with their matched population-based control group ($p=0.001$).

*(B) Patients with moderate–end-stage lung disease had overall a lower physical capacity than their matched controls ($p<0.001$). * $p<0.05$, ** $p<0.01$, *** $p<0.001$.*

5.2 Paper II: Muscle endurance, strength and active range of motion

Patients with SSc had reduced muscle endurance, when measured with FI-2, in both shoulder flexion as well as hip flexion in comparison with reference values. Differences in age groups are presented in Figure 3 A and B. Patients with moderate–end-stage lung disease had lower muscle endurance in both shoulder- and hip flexion than patients with no–mild lung disease (Table 6). No differences in muscle endurance were found between patients with lcSSc and dcSSc.

Muscle strength, as assessed by the TST, in the lower extremities were overall lower in patients, as well as in both lcSSc and dcSSc, and, no–mild and moderate–end-stage lung disease in comparison with reference values (Table 7). No differences in muscle strength in the lower extremities were found between lcSSc and dcSSc but patients with moderate–end-stage lung disease needed longer time to complete the test compared with patients with no–mild (Table 6).

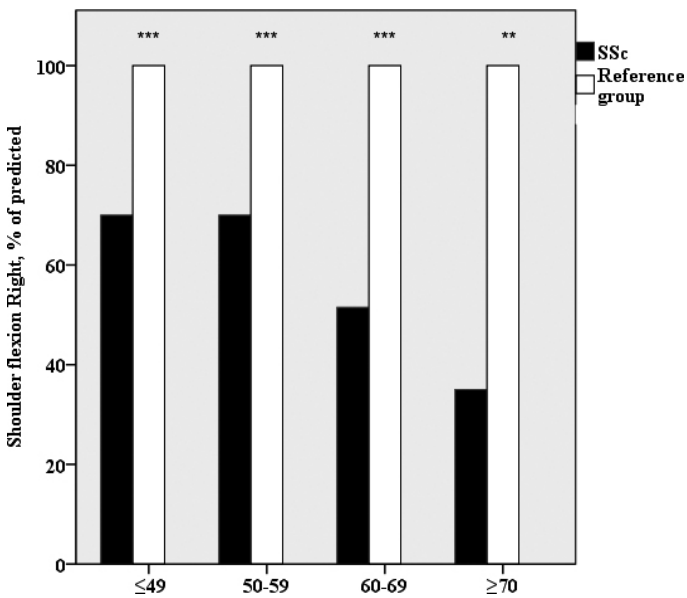

Figure 3 A. *Muscle endurance in shoulder flexion in right side in patients with systemic sclerosis (SSc) and reference group divided in different age groups. The values for shoulder flexion muscle endurance % of predicted according to Functional Index 2 in median.*
** p<0.05, **p<0.01, ***p<0.001.*

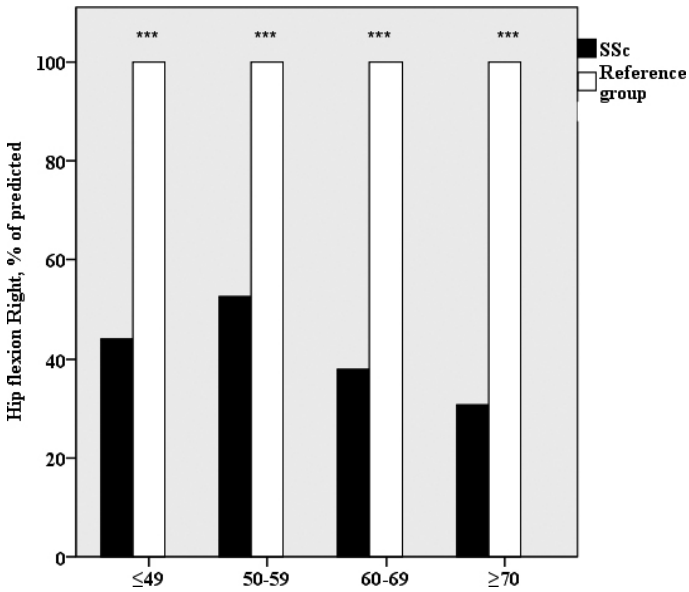

Figure 3 B. *Muscle endurance in hip flexion in right side in patients with systemic sclerosis (SSc) and reference group divided in different age groups. The values for hip flexion muscle endurance % of predicted according to Functional Index 2 in median. * p<0.05, **p<0.01, ***p<0.001.*

Table 6. Muscle endurance in shoulder- and hip flexion according to Functional Index 2 (FI-2), and muscle strength in lower extremities, as measured with Timed-Stand Test (TST), in patients with systemic sclerosis (SSc) stratified by subtypes defined by skin involvement (limited or diffuse SSc) and subgroups defined by extent of lung disease (no–mild or moderate–end-stage).

	All patients (n=205)	**lcSSc (n=169)**	**dcSSc (n=36)**	**p-value**	**No–mild lung disease (n=116)**	**Moderate–end-stage lung disease (n=82)**	**p-value**
Shoulder flexion endurance sum score, FI-2 %	50 (27–92)[8]	51 (28–94)[7]	42 (22–81)[1]	0.29	57 (33–99)[2]	39 (21–71)[6]	**0.01**
Hip flexion endurance sum score, FI-2 %	40 (25–79)[11]	40 (25–91)[9]	42 (24–61)[2]	0.49	48 (28–100)[2]	35 (20–70)[8]	**0.01**
TST, Sec	21 (17–27)[24]	21 (17–26)[18]	23 (18–29)[6]	0.59	19 (16–25)[13]	25 (18–30)[9]	**0.001**

Values are presented as median (IQR). lcSSc: limited cutaneous SSc; dcSSc: diffuse cutaneous SSc; No–mild lung disease: Medsger disease severity score 0–1; Moderate–end-stage lung disease: Medsger disease severity score 2–4; FI-2%: % of predicted Functional Index-2; TST: Timed-Stands Test (in seconds); [n]=missing numbers. Due to missing data, in diffusing capacity of the lung for carbon monoxide and/or forced vital capacity, 7 patients could not be classified as having no–mild or moderate–end-stage lung disease.

Table 7. Timed-Stands Test (TST) in patients with systemic sclerosis (SSc) stratified by subgroups defined by skin involvement (limited or diffuse SSc) and extent of lung disease (no–mild or moderate–end-stage) in comparison with predicted reference values.

	TST, Seconds	Predicted reference values TST, Seconds	p-value
All patients (n=205)	21 (17–27)[24]	17 (15–18)	**<0.001**
LcSSc (n=169)	21 (17–26)[18]	17 (16–18)	**<0.001**
DcSSc (n=36)	25 (18–29)[6]	17 (14–18)	**<0.001**
No–mild (n=116)	19 (16–25)[13]	17 (15–18)	**<0.001**
Moderate–end-stage (n=82)	25 (18–30)[9]	17 (16–18)	**<0.001**

Values are presented as median (IQR). LcSSc: limited cutaneous SSc; dcSSc: Diffuse cutaneous SSc; No–mild lung disease: Medsger disease severity score 0–1; Moderate–end-stage lung disease: Medsger disease severity score 2–4; [n]=missing numbers. Due to missing data, in diffusing capacity of the lung for carbon monoxide and/or forced vital capacity, 7 patients could not be classified as having no–mild or moderate–end-stage lung disease.

Patients with SSc had lower shoulder-arm AROM in both right (p=0.003) and left (p=0.001) compared with reference values (Table 8). A difference in sum score was found between patients with lcSSc 57 (52–60) and dcSSc 53 (48–57) where those with dcSSc had more impaired AROM (p=0.003). No differences were found between patients with no–mild and moderate–end-stage lung disease.

Table 8. Functional Shoulder Assessment (FSA) in patients with systemic sclerosis (SSc) and reference group stratified by different age groups.

		FSA, right, 4–24 points	p-value	FSA, left, 4–24 points	p-value
All age groups	SSc (n=205) Reference group B (n=246)	22 (20–24)[2] 23 (22–24)[3]	**0.003**	23 (20–24)[2] 23 (22–24)[3]	**0.001**
Ages ≤49	SSc (n=44) Reference group B (n=41)	22 (20–24)[2] 23 (22–24)[2]	0.42	24 (22–24)[2] 24 (23–24)	0.12
Ages 50–59	SSc (n=58) Reference group B (n=23)	23 (21–24) 23 (23–24)	0.26	23 (21–24) 23 (23–24)	0.28
Ages 60–69	SSc (n=54) Reference group B (n=74)	22 (19–24) 23 (23–23)[2]	**0.002**	23 (20–24) 23 (23–24)[3]	**0.008**
Ages ≥70	SSc (n=49) Reference group B (n=108)	21 (20–23) 22 (21–23)[1]	**0.001**	21 (19–23) 23 (21–24)	**<0.001**

FSA: Functional Shoulder Assessment (4–24 points for the four included tasks: hand-raising, hand-to-opposite-shoulder, hand-behind-back and hand-to-neck); The values for FSA are presented as points; [n]=missing numbers. Reference group B is collected from [110].

5.3 Paper III: Experiences of physical activity and exercise

From informant's voiced experiences three themes emerged; **Essential for life and health**, **Disease-related and other hindrances**, and, **Own understanding about PA/exercise and support from healthcare.** Eight categories were identified. Themes and categories are presented in Figure 4.

The first theme, **Essential for life and health**, consisted of three categories; *Diminishes symptoms and is as effective as pharmaceuticals, Reduces fear of deterioration*, and, *Feeling healthy and satisfied with oneself.*

In the category *Diminishes symptoms and is as effective as pharmaceuticals* it was expressed that PA/exercise was preferred as treatment instead of pharmaceuticals, mainly due to the positive effects on both physical and mental well-being. Especially improved blood circulation after PA/exercise was highlighted as an important result even though it was also voiced that the blood circulation initially could get worse during PA/exercise. Additionally, there were no severe side effects of PA/exercise even though pharmaceuticals sometimes were needed to treat disease symptoms.

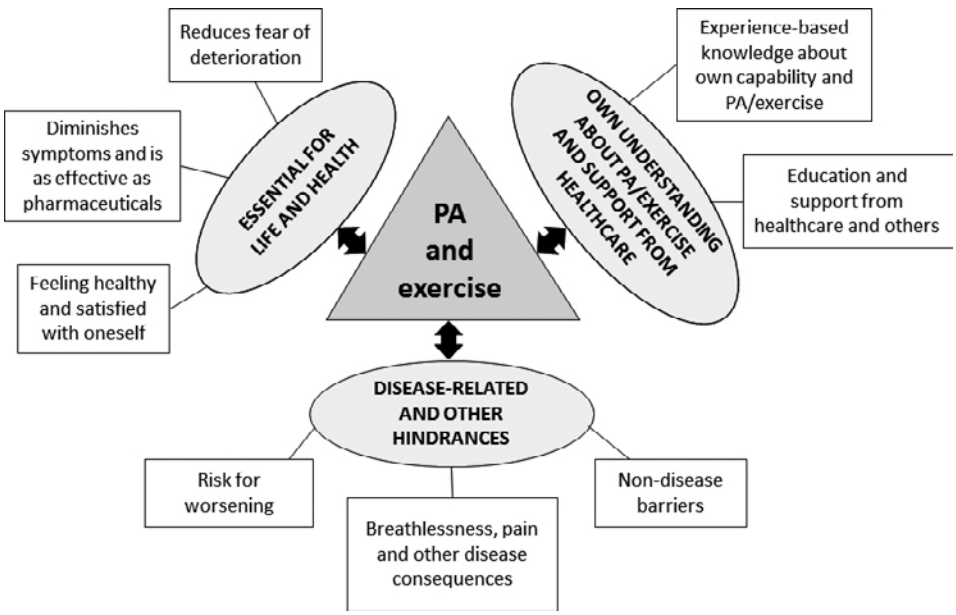

Figure 4. *Physical activity (PA) and exercise and the connection to the three Themes (oval shapes) and their categories.* ***Bold*** *arrows between central triangle and ovals indicate suggested mutual relationship.*

Presented examples of quotes are followed by the informants' specific identification code, i.e. I-I, no–mild lung disease (Informant I which has SSc with no–mild lung disease).

> *– As soon as one starts to work [spinning class] and get the circulation working, it takes a few minutes, but then it speeds up and it sort of remains until at least the next day, every so often two days (I-I, no–mild lung disease)*

> *– I don't want to take…medication. Somehow, I have a vision that I must get starting, more and better, with my exercise in order to, maybe sometime in the future, need not to take the medication (I-M, no–mild lung disease)*

Fear of worsening was an incentive to start, or continue, PA/exercise as expressed in the category *Reduces fear of deterioration.* The improved aerobic capacity and muscle strength after PA/exercise led to an increased sense of safety and it helped to reduced fear of deterioration. A need to maintain regular physical activities to have a long life worth living, and to be able to continue doing activities were recognised as motivating for PA/exercise.

> *– The more exercise I get, the better my health and bigger opportunities to survive longer. I don't want die. It's now that my life has started, somehow (I-O, moderate–end-stage lung disease)*

In the category *Feeling healthy and satisfied with oneself* it was expressed that PA/exercise installed both a physical and emotional state of healthiness and wellness, which gave a sense of being alive. Feelings of increased belief in oneself and increased self-esteem were phrased after PA/exercise, even when experiencing severe breathlessness. Muscle soreness was also experienced as something positive as it both was a proof that the exercises had paid off and that it diverted focus from other disease-related pain.

> *– You feel, you get a diagnosis, that means you get labelled as sick. But when you exercise you don't notice it, instead you feel healthier, when you have exercised, and everything worked out fine (I-L, no–mild lung disease)*

> *– Interviewer: What is the strongest feeling of physical activity that you can think of? Oh, you feel healthy. That's the best, …Yes, I think so, strong, vital, you can do more, enjoys life (I-N, moderate–end-stage lung disease)*

The second theme, **Disease-related and other hindrances**, consisted of three categories; *Breathlessness, pain and other disease consequences limit, Risk of worsening,* and, *Non-disease barriers.*

In the first category *Breathlessness, pain and other disease consequences limit*, typical and expected disease-related symptoms and problems were stated. Breathlessness, pain of various origin, and tight skin as well as tiredness were experienced as both barriers to, and consequences from PA/exercise.

> *– But it's the breathing that limits me the most [at PA] (I-F, moderate–end-stage lung disease)*

> *– Sometimes I think, if I hadn't these troubles [pain] with the feet...I would do much more, I would run, I would walk, and I would do so much more than I do today (I-B, no–mild lung disease)*

In the *Risk of worsening* expressions about negative consequences from PA/exercise were voiced. Shortness of breath was perceived as frightening and too high intensity exercise could cause, and worsen, symptoms like pain and digital ulcers.

> *– Sometimes I go all in [exercise] and that leads to [severe] muscle soreness, in scleroderma that is terribly painful (I-O, moderate–end-stage lung disease)*

> *– It's almost as if I'm counting how long they [hands] are white [when Nordic walking] because I'll think, please don't become digital ulcers now… because they are painful (I-H, no–mild lung disease)*

Non-disease barriers such as lack of time and lack of motivation as well as cold weather, not only outdoors, were experienced as barriers to PA/exercise. Furthermore, distance to and access to parking lots could make accessibility to health-care providers and gyms more difficult. Financial aspects like travel expenses and fees when visiting the physiotherapist were considered as barriers.

> *– When life is fully scheduled, should I do as the others and ask to be partially on sick-leave and maybe take care of my health and that maybe isn't such a bad idea but… I'm not there today (I-E, moderate–end-stage lung disease)*

> *– [Barriers] When it comes down to systemic sclerosis I think more support to exercises, from the government, more money to training sessions with the physiotherapist or to gyms (I-N, moderate–end-stage lung disease)*

The third and final theme, **Own understanding about PA/exercise and support from healthcare**, consisted of two categories; *Experience-based knowledge about own capability and PA/exercise,* and, *Education and support from healthcare and others.*

In *Experience-based knowledge about own capability and PA/exercise,* it was expressed that knowledge about own physical limitations, as well as experience of muscle strengthening exercises were beneficial as it both made exercising easier and reduced the risk of self-inflicted injury. By making adaptations to intensity, by exercising indoors when cold outside, or biking instead of running, and, using protective gloves or special soles in the shoes, made PA/exercise easier even when having a more severe form of SSc. Also, the need of analgesics or supplemental oxygen was highlighted as it sometimes made PA/exercise possible to perform.

> *– I don't run anymore, because the time it takes, to warm-up and get the circulation starting, during this time I get Raynaud…when it's this cold outside, and that's not good. So now one has to walk and run on a treadmill or bike on a spinning-bike instead of going outside (I-I, no–mild lung disease)*

> *– But you need four liters [supplemental oxygen] when you move around? Yes, five and a half when I'm sitting and doing my exercises. Interviewer: And you can feel exactly how much you need? Oh, yes (I-D, moderate–end-stage lung disease*)

In the category *Education and support from healthcare and other* informants it was expressed that information and support from physiotherapists was beneficial. Both general information and specific advices were appreciated even if not all expressed that they had received, needed or wanted information or support about PA/exercise. Support from other, like friend and family, and phone applications, also facilitated PA/exercise.

> *– The physiotherapy kick-start me into exercising when I've fallen behind. Then I go there for like three weeks, and this get me started… It makes me happy (I-O, moderate–end-stage lung disease)*

> *– [Not received information about the benefits of exercise in SSc] …I like to read about these processes in the blood vessels. It's quite complicated…, but when you read through it you understand that you can improve, a small part of it by exercise. So, I have done it anyway (I-I, no–mild lung disease)*

5.4 Paper IV: Health-related quality of life

Patients with SSc had lower HRQoL, in all eight domains of the SF-36, when compared with age- and gender-matched reference values (Figure 5). Both PCS and MCS were lower than reference values ($p<0.001$). Patients with no–mild ($p<0.01$–0.001) and moderate–end-stage lung disease ($p<0.001$) had lower scores than their respective reference values (Figure 5), likewise did both groups have lower PCS ($p<0.05$–0.001) and MCS ($p<0.001$) than their respective reference values.

Patients with no–mild lung disease had better HRQoL than patients with moderate–end-stage lung disease ($p<0.05-<0.001$) except for the mental health (Figure 5), and the PCS was higher ($p<0.001$), but no differences were found in the MCS between the groups ($p=0.2$).

Self-reported anxiety did not differ between groups but depressive symptoms, as measured with HAD, were higher, 4 (2-7), in the group with moderate–end-stage lung disease, compared with 3 (1-7) in no–mild ($p<0.05$).

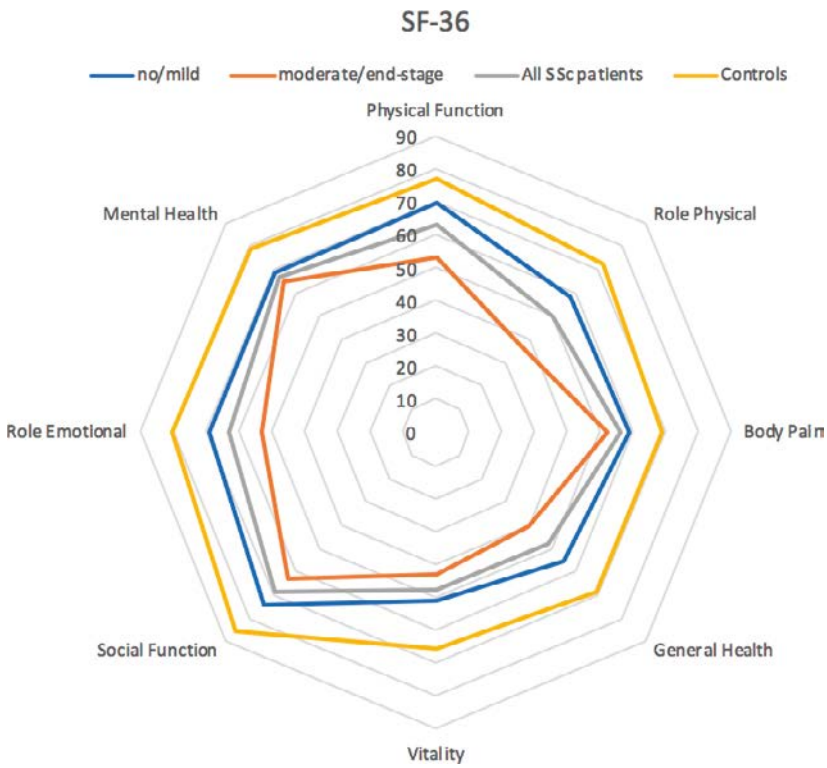

Figure 5. *Radar chart of the eight dimensions of Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) in Swedish general population, 279 patients with systemic sclerosis (SSc), 156 SSc-patients with no–mild and 115 with moderate–end-stage lung disease. The age-and gender matched reference values are from the general Swedish population [112]. In each area the scores range from 0 (worst) to 100 (best). Significant differences were found between all patients with SSc and their controls in all domains ($p<0.001$), as well as between patients with no–mild and with those with moderate–end-stage lung disease ($p<0.0001 – 0.036$) except in the mental health domain ($p=0.12$).*

The total sample of patients with SSc had relatively low disability-scores, 0.38, as measured with the HAQ-DI. Highest disease-specific disability on the VAS was RP, 44 mm, followed by General, 29 mm, Pain, 23 mm, and both Dyspnoea and Gastrointestinal, 12 mm and last digital ulcers, 2 mm.

Patients with no–mild lung disease had HAQ-DI 0.38 whereas moderate–end-stage had 0.63 ($p<0.001$). Patients with moderate–end-stage lung disease had more problems on VAS General ($p<0.001$) and VAS dyspnoea ($p<0.001$) than patients with no–mild lung disease (Table 9).

Table 9. Disability in patients with systemic sclerosis as defined by lung disease (no–mild or moderate–end-stage).

	No–mild lung disease (n=156)	**Moderate–end-stage lung disease (n=115)**	**p-value**
HAQ-DI (0-3 points)	0.38 (0-0.78)[2]	0.63 (0.13-1.38)[2]	**0.001**
VAS-General	21 (8-46)[11]	38 (20-56)[8]	**<0.0001**
VAS-Dyspnoea	3 (0-26)[8]	31 (7-72)[6]	**<0.0001**
VAS-RP	42 (15-77)[8]	48 (16-74)[6]	0.97
VAS-Digital ulcers	2 (0-16)[14]	4 (0-21)[10]	0.28
VAS-Pain	20 (1-48)	30 (4-54)[1]	0.14
VAS-Gastrointestinal	8 (0-50)[25]	21 (2-59)[27]	0.09

Values presented as median (IQR). HAQ-DI: Health Assessment Questionnaire Disability Index; VAS: visual analogue scale, 0-100 mm; RP: Raynaud's phenomenon; [n]=missing numbers.

Only 30% of the patients with SSc reported they had been PA on a low-moderate intensity the past six months on 6-7 days/week. More patients with no–mild lung disease (34%) than moderate–end-stage (24%) reported they were PA on a low-moderate intensity ($p<0.05$).

More than half, 52%, of patients with SSc reported that they never or irregularly had exercised the past year, and, 22% had exercised ≥3times/week. More patients with moderate–end-stage lung disease (60%) never or irregularly exercised in contrast to patients with no–mild (45%) ($p<0.05$), there were also fewer patients with moderate–end-stage lung disease that exercised ≥3times/week (15%) than in the group with no–mild (28%) ($p<0.05$).

A difference in self-reported physical capacity was found overall between patients with no–mild lung disease and moderate–end-stage ($p<0.001$) (Figure 6).

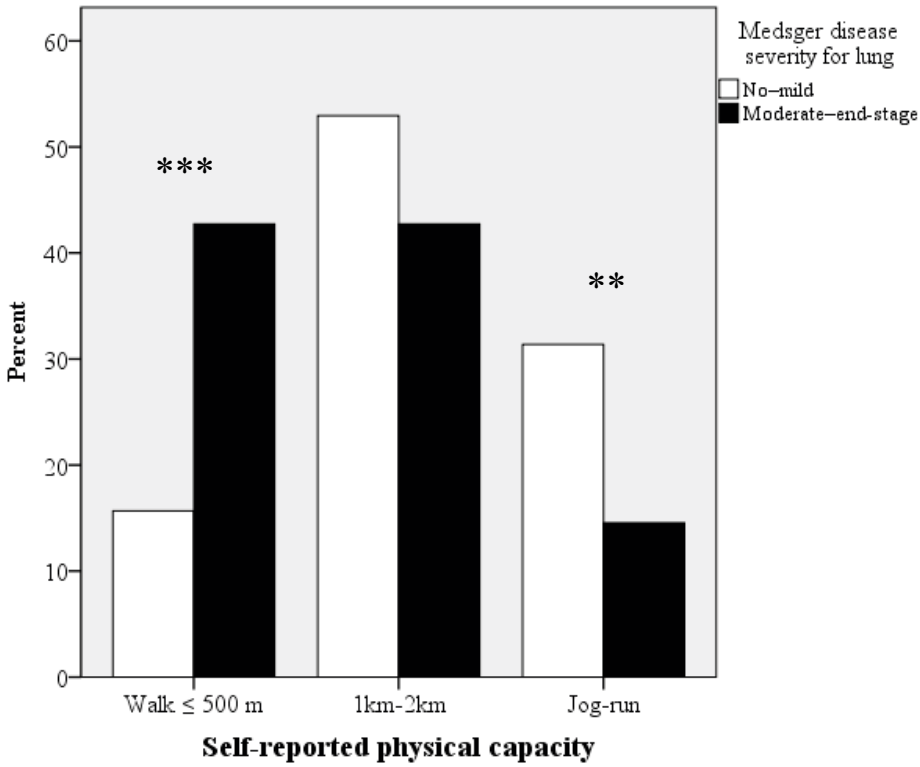

Figure 6. *Self-reported physical capacity in patients with systemic sclerosis divided into no–mild and moderate–end-stage lung disease. Significant differences between groups were revealed in walking ≤ 500 meters ($p<0.001$) and jog-running ($p=0.002$).*

As expected, there was a strong correlation between SF-36 PCS and HAQ-DI, moderate correlations between SF-36 PCS and self-reported physical capacity, VAS General, VAS Pain, and VAS Dyspnoea. There were low correlations between PCS and arthritis/arthralgia, the Medsger disease damage for lung, HADd, DLCO%, FVC% and VAS Gastrointestinal.

The SF-36 MCS correlated moderately with both HADa and HADd, low with VAS General, VAS Dyspnoea and VAS Pain.

Correlations between SF-36 PCS, MCS and variables of interest, in the two sub-groups based on lung disease, are presented in Table 10.

Table 10. Correlations between the composite scores from SF-36 (Physical Component Score and Mental Component Score) with clinical characteristics and disability.

	No–mild lung disease (n=156)		**Moderate–end-stage lung disease (n=115)**	
	PCS	**MCS**	**PCS**	**MCS**
Arthritis/Arthralgia (%)	**-0.46** ***	-0.22**	-**0.29** **	0.03
Medsger disease damage				
Heart	-0.11	-0.02	**-0.26** **	0.04
HAQ-DI	**-0.70** **	-0.23 **	**-0.70** **	-0.13
VAS-General	**-0.49** **	**-0.49** **	**-0.47** **	**-0.36** **
VAS-Dyspnoea	**-0.53** *	**-0.26** **	**-0.34** **	-0.24 **
VAS-RP	-0.01	-0.17 *	**-0.33** **	-0.03
VAS-Pain	**-0.52** *	-0.23 **	**-0.49** **	-0.19 *
VAS-Gastrointestinal	-0.24 **	-0.24 **	**-0.32** **	-0.17
Self-reported physical capacity, overall	**0.51** **	-0.18 *	**0.55** **	0.03
HADa	-0.15	**-0.62** **	0.02	**-0.57** **
HADd	**-0.37** **	**-0.64** **	-0.25	**-0.62** **

SF-36: Medical Outcome Study Short-Form 36; PCS: physical component score; MCS: mental component score; HAQ-DI: Health Assessment Questionnaire Disability Index; VAS: visual analogue scale 0-100 mm; RP: Raynaud's phenomenon; HADa/HADd, Hospital Anxiety and Depression scale, subitem anxiety and depression. Spearman´s correlation coefficients interpretation: 0.00-0.25: little if any; 0.26-0.49: low; 0.5-0.69: moderate; 0.7-0.89: high; 0.9-1: very high; **bold** numbers indicate results ≥0.26; * p<0.05, ** p<0.01, *** p<0.001.

6 DISCUSSION

6.1 Main findings

The overarching aim of this Thesis was to increase the knowledge of physical function, physical activity, and quality of life in patients with SSc with different degrees of lung disease. Even though patients with SSc did report lower physical capacity and more limiting factors for PA as well as that it was more common among the patients to report that they "never exercised" compared to age- and gender-matched controls, no differences were seen in self-reported PA nor time spent sitting, regardless of lung disease (**Paper I**). Patients with SSc had a markedly reduced muscle endurance in upper and lower extremities, and a reduced muscle strength in the lower extremities. Patients also had a somewhat impaired AROM in the shoulder-arms, especially patients older than 60 years. Patients with dcSSc had more impaired AROM in the shoulder-arms than lcSSc. There were no differences in muscle function between patients with lcSSc and dcSSc but patients with moderate–end-stage lung disease had less muscle endurance in both shoulder- and hip flexion as well as lower muscle strength in the lower extremities than patients with no–mild lung disease (**Paper II**). In **Paper III** informants with SSc experienced that PA/exercise was essential for life and health and that it reduced fear of deterioration, and, installed a feeling of health and satisfaction. Disease-related and other hindrances like shortness of breath and pain were problematic. An own understanding about PA/exercise, and support from healthcare was facilitating. Further it was expressed that information/education and support was both needed and beneficial. In **Paper IV** we showed that patients with SSc overall had a low HRQoL. Patients with moderate–end-stage lung disease had lower HRQoL and physical capacity as well as more depressive symptoms, disabilities and disease damage than patients with no–mild lung disease. Patients with moderate–end-stage lung disease were also less PA and exercised less.

6.2 Physical activity and exercise

In Paper I, self-reported PA/exercise were assessed and found to be lower than in age- and gender-matched population-based controls. Patients with moderate–end-stage lung disease reported lower levels of PA/exercise than those with no–mild lung disease in Paper IV.

The reported levels of PA on a low-moderate intensity 6-7 days/week the past six months are low among patients with SSc (Paper I). Unfortunately, even fewer patients in the group with moderate–end-stage lung disease reported that they were PA on low-moderate intensity 6-7 days/week the past six months (Paper IV). Similar indications of less regular exercise were seen in both groups, with the exception in patients with no–mild lung disease where slightly more patients reported that

they exercised ≥3 times/week. However, it is encouraging to see, in Paper IV, that more patients in both groups report they have a physical capacity allowing them to jog-run. These differences may be explained by the fact that during the recent years of inclusion of patients into the research SSc-cohort at Karolinska, several patients have been diagnosed quite early after symptom onset, and thus probably have less overall disease damage. The higher levels of self-reported physical capacity are encouraging and may reflect a shift in knowledge among the general population, as well as among patients with rheumatic diseases, in that exercise is beneficial. This hypothesis is supported by voiced expressions in Paper III, where it was expressed that PA/exercise could prolong their lives. It was also expressed that physical abilities had to be maintained or they would be lost. Feelings of inquietude were expressed when being inactive whereas senses of joy, increased self-esteem and increased health- and wellness were experienced after PA/exercise.

6.3 Patients experiences of physical activity and exercise

According to the shifting perspectives model of chronic illness [117], *living with a chronic illness is an ongoing, continually shifting process in which people experience a complex dialectic between themselves and their "world"*. The perspective of chronic illness determines how individuals/patients react to the disease, themselves, healthcare professionals as well as in situations that are affected by the illness, like social interactions and work. It is the perception of reality that is the kernel of how individuals/patients interpret, and respond, to their illness [117]. This shifting between putting the illness, or the wellness, in the foreground are different perspectives on how one may change in perception. Often do newly diagnosed persons have an illness perspective that has a utilitarian, or protective, function. The perspective of having wellness in the forefront is said to be using the illness as an opportunity to have a meaningful change in the relations and interactions with others. As seen in some of the phrased experiences in Paper III, as in the theme **Reduces fear of deterioration**, as well as in **Feeling healthy and satisfied with oneself**, the perspective of having the wellness in the foreground seems to be the most common approach to the disease, at least in this small group of patients with SSc.

Physical inactivity and sedentarism are central problems in patients with COPD where inactivity is reported to play a crucial role in the development of co-morbidities [118]. Regardless of disease severity, a sedentary lifestyle is present in all stages of COPD, and worsens as the disease severity progresses [118]. Problems with inactivity have previously been presented in patients with SSc [66]. As previously mentioned, the aims of rehabilitation in rheumatic diseases are, beside control of inflammatory processes and prevention of further disease damage, to maintain physical function and participation in society [74]. As in pharmacological treatment the rehabilitation process needs to start early after disease onset, be individualized and needs-driven. Furthermore, interventions and agreements between healthcare professionals and

patients' need to be followed up, evaluated and continue as long as the demand remains. These statements are echoed in Paper III where information/support from physiotherapists was considered as beneficial, especially early after disease-onset. Likewise, a need of individualized information about PA/exercise were sought after. The possibility to meet the physiotherapist when needed gave a noticeable boost, a kick-start, when having fallen behind. These expressions are coinciding with the statements in MoRR, that rehabilitation ought to include also PA/exercise that are adapted to the patient's needs. Likewise, help with pain/tiredness/anxiety/depression symptoms and problems with sleep [74].

Fatigue has previously been reported to be a major problem in SSc [52,119]. In Paper III the informants did not express themselves as having problems with fatigue, instead they used wordings like tired and tiredness. As no question in the interview guide was formulated to gain deeper insight into this problem the possible influence of fatigue on PA/exercise could not be explored.

6.4 Physical function

Paper II includes as far as we know the largest structured assessments of muscle endurance, muscle strength and AROM by use of FI-2, TST and FSA, done in patients with SSc.

Others have recently shown significantly lower extremity isokinetic muscle strength compared to healthy controls [120]. The FI-2 was used to measure dynamic repetitive muscle endurance in two muscle groups, shoulder- and hip flexion. The notably low muscle endurance, regardless disease subphenotype or degree of lung disease, clearly represent a major problem for most patients with this chronic disease. In myositis comparable, low levels of FI-2 shoulder- and hip flexion have recently been presented [121]. In another study, on patients with newly diagnosed myositis, the muscle endurance was lower than in our patients with SSc. The FI-2 was able to detect both worsening and improvements in muscle endurance at six and 12 months after diagnosis [122]. Among patients with ILD adaptations to a sedentary lifestyle is common behaviour, which in turn leads to a detrimental effect on muscle function. Not only is respiratory muscle function impaired, but also lower extremity muscle strength is reduced, especially in the quadriceps [123]. In patients with advanced ILD significantly worse muscle strength in the lower extremities, and worse results on functional muscle tests like the Timed Up and Go in comparison with healthy controls, have been presented. However, no differences were seen in the arms [124]. This is similar to our findings, in where patients needed significantly longer time to complete the TST, especially in the group with moderate–end-stage lung disease, where 60% of the patients had lung fibrosis. Furthermore, in Paper II we also noticed that our patients with SSc only had a muscle endurance of 40 % of predicted values in the hip flexion but 50 % in shoulder flexion.

6.5 Health-related quality of life

As previously shown, HRQoL is reduced in patients with SSc [59]. Furthermore, patients with SSc seems to have lower SF-36 scores in several of the domains in comparison with other chronic ailments like heart disease, hypertension and diabetes and also depression [125]. In Paper IV we showed that patients with moderate–end-stage lung disease had lower HRQoL than those with no–mild which is not surprising as they also have more disease damage, longer disease duration and reported lower physical capacity than patients with no–mild lung disease. Earlier studies have shown that patients with dcSSc have more severe disease manifestations [1], similar to our findings in the patients with moderate–end-stage lung disease. The PCS in our cohort with moderate–end-stage lung disease was similar with patients with SSc and PAH in another study [126], where they also found high correlations between a dyspnoea questionnaire and SF-36 PCS. Likewise, another study reported that the FVC is a significant independent predictor of disability/function (HAQ) and physical HRQoL [127]. Interestingly, we found higher associations between VAS dyspnoea and the PCS in patients with no–mild lung disease than in the group with moderate–end-stage. This could be due to that patients with no–mild lung disease had a shorter disease duration and that they found dyspnoea as an ominous symptom that can indicate a worsening of the disease and something that might hinder an active life style. Another way to look at this is that patients with moderate–end-stage lung disease have several other disease-related issues, like RP or gastrointestinal problems hindering PA, and that they have adapted to a sedentary lifestyle, and therefore dyspnoea is a lesser problem. In Paper III it was expressed that limited ability to breath was frightening. Breathlessness, pain and other disease consequences limit PA/exercise. An earlier study have also found that disease-related problems like tiredness interfering with life, pain and deformed hands makes ADL more difficult [128]. Deformed hands because of SSc naturally affect the possibilities to function adequately in ADL and this is shown in the HAQ-DI which was higher (more disability) among patients with moderate–end-stage lung disease, even though both patient groups had the same, high, correlation between HAQ-DI and PCS as seen in Paper IV. Here we only focused on differences in self-reported disability/function among patients with different degrees of lung involvement and not on cutaneous subphenotypes.

6.6 Scoring of lung disease severity

The use of the Medsger disease severity score has not previously been used as a dichotomous variable to categorize lung disease in patients with SSc. The reason we chose this way to divide patients with different degrees of lung disease is mainly because it provides an, overall, simple and clear distinction between subclinical and clinical cardiopulmonary symptoms. We hypothesized that it would be possible to distinguish patients with different degrees of lung involvement by this classification. Others have proposed different cut-offs based on lung disease.

Goh et al. [31] proposed a method based on findings from HRCT and FVC, with 70% as cut-off for staging ILD into limited or extensive disease. This method may be of use in patients with ILD only, but less feasible in patients with SSc that also can have reduced DLCO% and/or PAH. In the Scleroderma Lung study [61] which studied patients with SSc with active alveolitis, another approach was used. In this study the values for FVC% and DLCO% were divided into mild (>70% of predicted), moderate (50-70%), and severe (<50%), however, due to low number of eligible patients in the severe FVC group, severe and moderate groups were combined for analysis. For some reason, also groups with mild and moderate DLCO were combined.

In papers I, II and IV we found that the dichotomization of the Medsger disease severity score for the lung has been able to discriminate between patients with no–mild and moderate–end-stage lung disease as to both objective and self-reported variables.

In Paper I we used the term moderate–severe lung disease for all patients that had a disease damage score of 2, 3, and 4. In papers II-IV we changed to moderate–end-stage as we considered this to be a more correct way to describe the total variation in lung disease in our cohort.

6.7 Methodological considerations

In this Thesis both quantitative and qualitative methods were used to answer the research questions. Different statistical methods were therefore used. Most of the variables were non-normally distributed which prompted the use of non-parametric tests but to be able to compare our results with previous research we have calculated, and presented part of the results, by use of parametric statistical methods. For example, in Paper IV we used parametric presentation for result of SF-36. However, we did also use non-parametric methods to confirm our findings without relevant discrepancies between the two different approaches.

Considering the rarity of SSc the large sample sizes are a methodological strength, especially in Paper II and Paper IV. In Paper I the large cohort with patients with SSc and the well-matched population-based controls are the strengths of this study. On the other hand, we used self-reported questions and recall errors are common when reporting habitual activities on light to moderate intensity, like house-work and walking [129]. These types of activities are often under-reported which might be the case in our study. Self-reported data may not be as valid or reliable as data gathered by for example accelerometers used in a few studies in SSc [66,67]. Conversely, an accelerometer does not take into account if the participant is carrying bags and/or walks in stairs which naturally is more strenuous than just walking [130]. Several studies [101,131] have shown that objectively measured physical activities produced a different activity pattern and lower values in comparison

with frequently used self-reported questionnaires. These studies [101,131] had a relatively large dropout and it is likely that the individuals who completed the test were the most fit and/or motivated, alternatively that some participants had difficulties with handling the devices. Our study, on the contrary, had a very high response rate, >90% among patients in the SSc group and 98% in the control group which probably is because all participants were summoned to a visit at the clinic.

In Paper II, the relatively large number of missing data in the TST is a drawback. The reason for this problem is due to several factors: not all patients could complete the ten full stands because of weakness or were stopped because of incorrect performance such as using their hands to push up or to maintain balance. Others ended the test prematurely because of pain in hips and/or knees or because of severe dyspnoea. The 30-second sit-to-stand test [88] may be a more suitable test in future assessments, or clinical trials, as even if the test person only manages to complete a couple of repetitions it is still a valid result, whereas if the test person is not able to complete the ten full stands in TST no result is acquired.

In Paper III individual interviews were performed. Other researchers in SSc have used focus group discussions when investigating coping strategies among patients with SSc [132-134]. This approach let the researcher gather many individuals and take part of their experiences [135]. However, as SSc is such a rare and heterogenous disease we chose to do individual interviews in order to let the informants freely express their experiences. Also, it increased the anonymity of the informants. We believe this enhanced informants' ability to easily express their thoughts, beliefs and experiences without risk feeling subdued by others that may have been more vocal [105]. On the other hand, being part of a focus group can help to facilitate discussion among the informants, ease recollection of details and it can also help to characterise both divergent and common experiences [105].

One of the differences between standard calculations used in quantitative research and qualitative research is that qualitative research to a higher extent is dependent on skills and experiences among the researchers in the analysis of data [105]. To increase the trustworthiness of the analysis triangulation was done between the first Author and two senior researchers with experience of qualitative methodology. Discussion and confirmation of the findings were also done with the other co-authors as well as in a research group with experiences of both qualitative research and clinical care within the field of rheumatology. We find the results plausible but are aware that other researchers may discover, and interpret, other findings in the transcripts, but the content would still be the same. The transferability of our findings is to some extent dependent on other readers' experiences and contexts. We think that the diversity among our informants increases the trustworthiness of our findings.

In qualitative research the sample size depends on the richness in information gathered from the informants and the variety in the sample [108]. In paper III 16 interviews were conducted which we considered sufficient to achieve an adequate and plausible representation of experiences of PA/exercise in SSc. The strategic identification of informants is a strength as informants represented both women and men in various age, and with various diagnosis duration, lung involvement and disability. However, it is still possible that by performing additional interviews new information could be presented [104].

Among the individuals that were interviewed some were not native Swedish. We believe it to be a strength to have the possibility to include participants from other settings and cultural backgrounds even though there to some extent may be a language barrier. Similar language-related problems did occur in Paper IV where some patients were unable to answer the questionnaires and therefore could not be included in the study.

Regression analysis would have strengthened the results In Paper IV. We only used a method to quantify the relationship between variables. To be able to determine the strength, and direction, of the association between HRQoL and independent variables (e.g. Medsger disease damage, HAQ-DI, gender, age and physical capacity), we plan to perform regression analysis.

6.8 Concluding remarks and future perspectives

This Thesis has demonstrated that patients with SSc "never exercise" to a higher extent than population-based controls but overall, they were not less physically active than population-based controls. However, most patients do not reach the World Health Organization´s recommendations of physical activity (150 minutes of moderate-intensity aerobic physical activity throughout the week, or**,** do at least 75 minutes of vigorous-intensity aerobic physical activity throughout the week, or, an equivalent combination of moderate- and vigorous-intensity activity) [136]. Furthermore, the results showed that self-reported physical capacity were lower among patients with SSc compared to population-based population, and they have markedly low muscle strength and muscle endurance compared to reference values. Patients with moderate–end-stage lung disease also have lower self-reported physical capacity and more impairments in muscle strength and muscle endurance than those with no–mild lung disease, but surprisingly no differences were found between patients with lcSSc and dcSSc. Patients with SSc, including patients with both no–mild and moderate–end-stage lung disease experience PA/exercise as essential for life and health. There are different disease-related and other hindrances, but own understanding about PA/exercise and support from healthcare facilitated the possibilities to be physically active and exercise. Patients with moderate–end-stage lung disease have lower self-reported physical capacity, are

less PA/exercise, are more disabled, have a lower HRQoL and have more depression symptoms than patients with no–mild lung disease. The studies in this Thesis have contributed with new knowledge about how to develop future PA/exercise programs for patients with SSc, especially for those with more severe lung disease. The Thesis also shows the need of rheumatological rehabilitation for patients with SSc with focus on physical function, physical activity and exercise and HRQoL.

6.8.1 Conclusions Papers I – IV

In Paper I we conclude that even though patients with SSc reported lower physical capacity and more limiting factors for physical capacity, and more patients reported they "never exercised", than age- and gender-matched population-based controls, no differences in self-reported physical activity nor time spent sitting were found. Further development of physical activity programmes for patients with SSc, and especially for those patients that never exercise, or have physical impairments is needed.

In Paper II we drew the conclusion that patients with SSc have markedly reduced muscle endurance in both the upper and lower extremities, reduced muscle strength in the lower extremities, as well as an impaired AROM in the shoulder-arm girdles. Patients with moderate–end-stage lung disease had more impaired muscle endurance and strength than patients with no–mild lung disease but no differences were found between lcSSc and dcSSc. Not only muscle strength, but also dynamic muscle endurance needs to be measured in patients with SSc.

In Paper III we found that patients with SSc experienced that PA/exercise was essential for life and health. PA/exercise reduces fear of deterioration, but it was also expressed as a risk of worsening. Furthermore, disease-related and other hindrances like shortness of breath and pain were problematic. An own understanding about PA/exercise, and support from healthcare was facilitating. It was also expressed that information/education and support was both needed and beneficial. These findings add new knowledge to the effects of PA/exercise in SSc and what is perceived as facilitating and hindrances.

In Paper IV we conclude that patients with SSc and moderate–end-stage lung disease have a lower physical HRQoL, more depression symptoms, are more disabled, and additionally they have more overall disease manifestations. Patients with moderate–end-stage lung disease have also a lower physical capacity, are less PA and they exercise less than patients with no–mild lung disease.

6.8.2 Future research

Due to the rarity of SSc, planning and performing a multi-centre exercise approach would be of great value. The optimal way of exercising with the aim to increase both muscular strength and muscular endurance in patients with different degrees of lung disease needs to be further elucidated, especially in patients with moderate–end-stage lung disease.

Patients in the interview study expressed that physical exercise could increase blood circulation but whether positive long-term effects on blood circulation are achievable after PA/exercise needs to be further investigated, preferably in a randomized controlled trial. Possible outcome measures could be muscle biopsies and/or Power Doppler ultrasound to evaluate changes in capillary density, and, blood circulation.

The impact of pain and fatigue on PA/exercise, and vice versa, also needs to be further investigated. It would also be interesting to further study how pain and fatigue is associated with different degrees of lung involvement, preferably with a qualitative approach.

Likewise, it would also be of interest to investigate if disability/function, HRQoL and anxiety/depression symptoms can be altered after participating in PA/exercise intervention, and what long-lasting effects can be gained in self-reported HRQoL, especially in patients with moderate–end-stage lung disease.

How the muscle strength and muscle endurance changes over time in SSc needs to be studied in a longitudinal study.

In parallel with the above efforts, a further development of the Swedish Rheumatology Quality register (SRQ) SSc module would be important. A combination of high-quality objective, and self-reported longitudinal, data would enhance the ability to understand long-term outcomes in SSc and to evaluate the results of current pharmacological as well as non-pharmacological treatments.

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8 REFERENCES

[1] Walker UA, Tyndall A, Czirjak L, Denton C, Farge-Bancel D, Kowal-Bielecka O, Muller-Ladner U, Bocelli-Tyndall C, Matucci-Cerinic M. Clinical risk assessment of organ manifestations in systemic sclerosis: a report from the EULAR Scleroderma Trials And Research group database. Ann Rheum Dis 2007;66:754-63.

[2] Hinchcliff M, Varga J. Systemic sclerosis/scleroderma: a treatable multi-system disease. Am Fam Physician 2008;78:961-8.

[3] Preliminary criteria for the classification of systemic sclerosis (scleroderma). Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Arthritis Rheum 1980;23:581-90.

[4] van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, Matucci-Cerinic M, Naden RP, Medsger TA, Jr., Carreira PE and others. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. Arthritis Rheum 2013;65:2737-47.

[5] LeRoy EC, Medsger TA, Jr. Criteria for the classification of early systemic sclerosis. J Rheumatol 2001;28:1573-6.

[6] Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH. Rheumatology. Philadelphia: Mosby/Elsevier; 2011.

[7] Denton CP, Khanna D. Systemic sclerosis. Lancet 2017;390:1685-99.

[8] Grassegger A, Pohla-Gubo G, Frauscher M, Hintner H. Autoantibodies in systemic sclerosis (scleroderma): clues for clinical evaluation, prognosis and pathogenesis. Wien Med Wochenschr 2008;158:19-28.

[9] Didier K, Bolko L, Giusti D, Toquet S, Robbins A, Antonicelli F, Servettaz A. Autoantibodies Associated With Connective Tissue Diseases: What Meaning for Clinicians? Front Immunol 2018;9:541.

[10] Steen VD. Autoantibodies in systemic sclerosis. Semin Arthritis Rheum 2005;35:35-42.

[11] Steen V, Domsic RT, Lucas M, Fertig N, Medsger TA, Jr. A clinical and serologic comparison of African American and Caucasian patients with systemic sclerosis. Arthritis Rheum 2012;64:2986-94.

[12] Hamaguchi Y. Autoantibody profiles in systemic sclerosis: predictive value for clinical evaluation and prognosis. J Dermatol 2010;37:42-53.

[13] Barnes J, Mayes MD. Epidemiology of systemic sclerosis: incidence, prevalence, survival, risk factors, malignancy, and environmental triggers. Curr Opin Rheumatol 2012;24:165-70.

[14] Andreasson K, Saxne T, Bergknut C, Hesselstrand R, Englund M. Prevalence and incidence of systemic sclerosis in southern Sweden: population-based data with case ascertainment using the 1980 ARA criteria and the proposed ACR-EULAR classification criteria. Ann Rheum Dis 2014;73:1788-92.

[15] Medsger TA, Jr., Bombardieri S, Czirjak L, Scorza R, Della Rossa A, Bencivelli W. Assessment of disease severity and prognosis. Clin Exp Rheumatol 2003;21:S42-6.

[16] Clements P, Lachenbruch P, Siebold J, White B, Weiner S, Martin R, Weinstein A, Weisman M, Mayes M, Collier D and others. Inter and intraobserver variability of total skin thickness score (modified Rodnan TSS) in systemic sclerosis. J Rheumatol 1995;22:1281-5.

[17] Benedek TG, Rodnan GP. The early history and nomenclature of scleroderma and of its differentiation from sclerema neonatorum and scleroedema. Semin Arthritis Rheum 1982;12:52-67.

[18] Bussone G, Mouthon L. Interstitial lung disease in systemic sclerosis. Autoimmunity Reviews 2011;10:248-55.

[19] Cottrell TR, Wise RA, Wigley FM, Boin F. The degree of skin involvement identifies distinct lung disease outcomes and survival in systemic sclerosis. Ann Rheum Dis 2014;73:1060-6.

[20] Sweiss NJ, Hushaw L, Thenappan T, Sawaqed R, Machado RF, Patel AR, Gomberg-Maitland M, Husain AN, Archer SL. Diagnosis and management of pulmonary hypertension in systemic sclerosis. Curr Rheumatol Rep 2010;12:8-18.

[21] Pauling JD, Saketkoo LA, Matucci-Cerinic M, Ingegnoli F, Khanna D. The patient experience of Raynaud's phenomenon in systemic sclerosis. Rheumatology (Oxford) 2018.

[22] Hughes M, Herrick AL. Digital ulcers in systemic sclerosis. Rheumatology (Oxford) 2017;56:14-25.

[23] Matucci-Cerinic M, Kahaleh B, Wigley FM. Review: evidence that systemic sclerosis is a vascular disease. Arthritis Rheum 2013;65:1953-62.

[24] Proudman SM, Stevens WM, Sahhar J, Celermajer D. Pulmonary arterial hypertension in systemic sclerosis: the need for early detection and treatment. Intern Med J 2007;37:485-94.

[25] Schoenfeld SR, Castelino FV. Evaluation and management approaches for scleroderma lung disease. Ther Adv Respir Dis 2017;11:327-40.

[26] Steen VD. The lung in systemic sclerosis. J Clin Rheumatol 2005;11:40-6.

[27] Hoffmann-Vold AM, Aalokken TM, Lund MB, Garen T, Midtvedt O, Brunborg C, Gran JT, Molberg O. Predictive value of serial high-resolution computed tomography analyses and concurrent lung function tests in systemic sclerosis. Arthritis Rheumatol 2015;67:2205-12.

[28] Tyndall AJ, Bannert B, Vonk M, Airo P, Cozzi F, Carreira PE, Bancel DF, Allanore Y, Muller-Ladner U, Distler O and others. Causes and risk factors for death in systemic sclerosis: a study from the EULAR Scleroderma Trials and Research (EUSTAR) database. Ann Rheum Dis 2010;69:1809-15.

[29] Racz H, Mehta S. Dyspnea due to pulmonary hypertension and interstitial lung disease in scleroderma: room for improvement in diagnosis and management. J Rheumatol 2006;33:1723-5.

[30] Willems LM, Kwakkenbos L, Leite CC, Thombs BD, van den Hoogen FH, Maia AC, Vliet Vlieland TP, van den Ende CH. Frequency and impact of disease symptoms experienced by patients with systemic sclerosis from five European countries. Clin Exp Rheumatol 2014;32:S-88-93.

[31] Goh NS, Desai SR, Veeraraghavan S, Hansell DM, Copley SJ, Maher TM, Corte TJ, Sander CR, Ratoff J, Devaraj A and others. Interstitial lung disease in systemic sclerosis: a simple staging system. Am J Respir Crit Care Med 2008;177:1248-54.

[32] Morales-Cardenas A, Perez-Madrid C, Arias L, Ojeda P, Mahecha MP, Rojas-Villarraga A, Carrillo-Bayona JA, Anaya JM. Pulmonary involvement in systemic sclerosis. Autoimmun Rev 2016.

[33] Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, Colby TV, Cordier JF, Flaherty KR, Lasky JA and others. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med 2011;183:788-824.

[34] Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P and others. Standardisation of spirometry. Eur Respir J 2005;26:319-38.

[35] Macintyre N, Crapo RO, Viegi G, Johnson DC, van der Grinten CP, Brusasco V, Burgos F, Casaburi R, Coates A, Enright P and others. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur Respir J 2005;26:720-35.

[36] Khanna D, Gladue H, Channick R, Chung L, Distler O, Furst DE, Hachulla E, Humbert M, Langleben D, Mathai SC and others. Recommendations for screening and detection of connective tissue disease-associated pulmonary arterial hypertension. Arthritis Rheum 2013;65:3194-201.

[37] Maddali-Bongi S, Del Rosso A. Systemic sclerosis: rehabilitation as a tool to cope with disability. Clin Exp Rheumatol 2016;34 Suppl 100:162-9.

[38] Sandqvist G, Eklund M, Akesson A, Nordenskiold U. Daily activities and hand function in women with scleroderma. Scand J Rheumatol 2004;33:102-7.

[39] Poole JL, Brandenstein J. Difficulty with daily activities involving the lower extremities in people with systemic sclerosis. Clin Rheumatol 2016;35:483-8.

[40] Hadj Said M, Foletti JM, Graillon N, Guyot L, Chossegros C. Orofacial manifestations of scleroderma. A literature review. Rev Stomatol Chir Maxillofac Chir Orale 2016;117:322-6.

[41] Avouac J, Clements PJ, Khanna D, Furst DE, Allanore Y. Articular involvement in systemic sclerosis. Rheumatology (Oxford) 2012;51:1347-56.

[42] Young A, Namas R, Dodge C, Khanna D. Hand Impairment in Systemic Sclerosis: Various Manifestations and Currently Available Treatment. Curr Treatm Opt Rheumatol 2016;2:252-69.

[43] Avouac J, Walker U, Tyndall A, Kahan A, Matucci-Cerinic M, Allanore Y, Miniati I, Muller A, Iannone F, Distler O and others. Characteristics of joint involvement and relationships with systemic inflammation in systemic sclerosis: results from the EULAR Scleroderma Trial and Research Group (EUSTAR) database. J Rheumatol 2010;37:1488-501.

[44] Balint Z, Farkas H, Farkas N, Minier T, Kumanovics G, Horvath K, Solyom AI, Czirjak L, Varju C. A three-year follow-up study of the development of joint contractures in 131 patients with systemic sclerosis. Clin Exp Rheumatol 2014;32:S-68-74.

[45] Rannou F, Boutron I, Mouthon L, Sanchez K, Tiffreau V, Hachulla E, Thoumie P, Cabane J, Chatelus E, Sibilia J and others. Personalized Physical Therapy Versus Usual Care for Patients With Systemic Sclerosis: A Randomized Controlled Trial. Arthritis Care Res (Hoboken) 2017;69:1050-9.

[46] Lima TR, Guimaraes FS, Silva LA, Silva DP, Menezes SL, Lopes AJ. Relationship between functional capacity, joint mobility and pulmonary function in patients with systemic sclerosis. J Bodyw Mov Ther 2015;19:17-24.

[47] Poole JL, New A, Garcia C. A comparison of performance on the Keitel Functional Test by persons with systemic sclerosis and rheumatoid arthritis. Disabil Rehabil 2017:1-4.

[48] Walker UA, Clements PJ, Allanore Y, Distler O, Oddis CV, Khanna D, Furst DE. Muscle involvement in systemic sclerosis: points to consider in clinical trials. Rheumatology (Oxford) 2017;56:v38-v44.

[49] Clements PJ, Furst DE, Campion DS, Bohan A, Harris R, Levy J, Paulus HE. Muscle disease in progressive systemic sclerosis: diagnostic and therapeutic considerations. Arthritis Rheum 1978;21:62-71.

[50] Lima TR, Guimaraes FS, Carvalho MN, Sousa TL, Menezes SL, Lopes AJ. Lower limb muscle strength is associated with functional performance and quality of life in patients with systemic sclerosis. Braz J Phys Ther 2015;19:129-36.

[51] Hughes M, Herrick AL. Raynaud's phenomenon. Best Pract Res Clin Rheumatol 2016;30:112-32.

[52] Sandusky SB, McGuire L, Smith MT, Wigley FM, Haythornthwaite JA. Fatigue: an overlooked determinant of physical function in scleroderma. Rheumatology (Oxford) 2009;48:165-9.

[53] Stamm TA, Mattsson M, Mihai C, Stocker J, Binder A, Bauernfeind B, Stummvoll G, Gard G, Hesselstrand R, Sandqvist G and others. Concepts of functioning and health important to people with systemic sclerosis: a qualitative study in four European countries. Ann Rheum Dis 2011;70:1074-9.

[54] Johnson SR, Glaman DD, Schentag CT, Lee P. Quality of life and functional status in systemic sclerosis compared to other rheumatic diseases. J Rheumatol 2006;33:1117-22.

[55] Rannou F, Poiraudeau S, Berezne A, Baubet T, Le-Guern V, Cabane J, Guillevin L, Revel M, Fermanian J, Mouthon L. Assessing disability and quality of life in systemic sclerosis: construct validities of the Cochin Hand Function Scale, Health Assessment Questionnaire (HAQ), Systemic Sclerosis HAQ, and Medical Outcomes Study 36-Item Short Form Health Survey. Arthritis Rheum 2007;57:94-102.

[56] Lumetti F, Barone L, Alfieri C, Silva M, Serra V, Delsante G, Sverzellati N, Ariani A. Quality of life and functional disability in patients with interstitial lung disease related to Systemic Sclerosis. Acta Biomed 2015;86:142-8.

[57] World Health Organization. Division of Mental Health and Prevention of Substance Abuse, World Health Organization 1997 – [cited 2019 March, 30]; Available from: https://www.who.int/mental_health/media/68.pdf.

[58] Sullivan M, Karlsson J, Ware JE, Jr. The Swedish SF-36 Health Survey--I. Evaluation of data quality, scaling assumptions, reliability and construct validity across general populations in Sweden. Soc Sci Med 1995;41:1349-58.

[59] Hudson M, Thombs BD, Steele R, Panopalis P, Newton E, Baron M. Health-related quality of life in systemic sclerosis: a systematic review. Arthritis Rheum 2009;61:1112-20.

[60] Frantz C, Avouac J, Distler O, Amrouche F, Godard D, Kennedy AT, Connolly K, Varga J, Matucci-Cerinic M, Allanore Y. Impaired quality of life in systemic sclerosis and patient perception of the disease: A large international survey. Semin Arthritis Rheum 2016;46:115-23.

[61] Khanna D, Clements PJ, Furst DE, Chon Y, Elashoff R, Roth MD, Sterz MG, Chung J, FitzGerald JD, Seibold JR and others. Correlation of the degree of dyspnea with health-related quality of life, functional abilities, and diffusing capacity for carbon monoxide in patients with systemic sclerosis and active alveolitis: results from the Scleroderma Lung Study. Arthritis Rheum 2005;52:592-600.

[62] Steen VD, Medsger TA, Jr. Severe organ involvement in systemic sclerosis with diffuse scleroderma. Arthritis Rheum 2000;43:2437-44.

[63] Nguyen C, Ranque B, Baubet T, Berezne A, Mestre-Stanislas C, Rannou F, Papelard A, Morell-Dubois S, Revel M, Moro MR and others. Clinical, functional and health-related quality of life correlates of clinically significant symptoms of anxiety and depression in patients with systemic sclerosis: a cross-sectional survey. PLoS One 2014;9:e90484.

[64] Nguyen C, Berezne A, Baubet T, Mestre-Stanislas C, Rannou F, Papelard A, Morell-Dubois S, Revel M, Guillevin L, Poiraudeau S and others. Association of gender with clinical expression, quality of life, disability, and depression and anxiety in patients with systemic sclerosis. PLoS One 2011;6:e17551.

[65] Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. Public Health Rep 1985;100:126-31.

[66] Battaglia S, Bellia M, Serafino-Agrusa L, Giardina A, Messina M, Cannizzaro F, Midiri M, Triolo G, Scichilone N. Physical capacity in performing daily activities is reduced in scleroderma patients with early lung involvement. Clin Respir J 2015.

[67] Mainguy V, Provencher S, Maltais F, Malenfant S, Saey D. Assessment of daily life physical activities in pulmonary arterial hypertension. PLoS One 2011;6:e27993.

[68] Liem SIE, Meessen J, Wolterbeek R, Ajmone Marsan N, Ninaber MK, Vliet Vlieland TPM, de Vries-Bouwstra JK. Physical activity in patients with systemic sclerosis. Rheumatol Int 2018;38:443-53.

[69] de Oliveira NC, dos Santos Sabbag LM, Ueno LM, de Souza RB, Borges CL, de Sa Pinto AL, Lima FR. Reduced exercise capacity in systemic sclerosis patients without pulmonary involvement. Scand J Rheumatol 2007;36:458-61.

[70] Morelli S, Ferrante L, Sgreccia A, Eleuteri ML, Perrone C, De Marzio P, Balsano F. Pulmonary hypertension is associated with impaired exercise performance in patients with systemic sclerosis. Scand J Rheumatol 2000;29:236-42.

[71] Veldhuijzen van Zanten JJ, Rouse PC, Hale ED, Ntoumanis N, Metsios GS, Duda JL, Kitas GD. Perceived Barriers, Facilitators and Benefits for Regular Physical Activity and Exercise in Patients with Rheumatoid Arthritis: A Review of the Literature. Sports Med 2015;45:1401-12.

[72] Fongen C, Sveaas SH, Dagfinrud H. Barriers and Facilitators for Being Physically Active in Patients with Ankylosing Spondylitis: A Cross-sectional Comparative Study. Musculoskeletal Care 2015;13:76-83.

[73] Thorpe O, Kumar S, Johnston K. Barriers to and enablers of physical activity in patients with COPD following a hospital admission: a qualitative study. Int J Chron Obstruct Pulmon Dis 2014;9:115-28.

[74] Alenius G-M, Avik A, Calander A-M, Lindqvist E, Teleman E. Stockholm: Rekommendationer för Modern ReumaRehabilitering MoRR (Recommendations for Modern Rheumatological Rehabilitation, MoRR), Svensk Reumatologisk Förening; 2019 - [cited 2019 March, 26]; Available from: http://svenskreumatologi.se/srfs-riktlinjer/.

[75] Willems LM, Vriezekolk JE, Schouffoer AA, Poole JL, Stamm TA, Bostrom C, Kwakkenbos L, Vliet Vlieland TP, van den Ende CH. Effectiveness of Nonpharmacologic Interventions in Systemic Sclerosis: A Systematic Review. Arthritis Care Res (Hoboken) 2015;67:1426-39.

[76] de Oliveira NC, Portes LA, Pettersson H, Alexanderson H, Bostrom C. Aerobic and resistance exercise in systemic sclerosis: State of the art. Musculoskeletal Care 2017;15:316-23.

[77] Oliveira NC, dos Santos Sabbag LM, de Sa Pinto AL, Borges CL, Lima FR. Aerobic exercise is safe and effective in systemic sclerosis. Int J Sports Med 2009;30:728-32.

[78] Alexanderson H, Bergegard J, Bjornadal L, Nordin A. Intensive aerobic and muscle endurance exercise in patients with systemic sclerosis: a pilot study. BMC Res Notes 2014;7:86.

[79] Pinto AL, Oliveira NC, Gualano B, Christmann RB, Painelli VS, Artioli GG, Prado DM, Lima FR. Efficacy and safety of concurrent training in systemic sclerosis. J Strength Cond Res 2011;25:1423-8.

[80] Poole JL. Musculoskeletal rehabilitation in the person with scleroderma. Curr Opin Rheumatol 2010;22:205-12.

[81] Mugii N, Hasegawa M, Matsushita T, Kondo M, Orito H, Yanaba K, Komura K, Hayakawa I, Hamaguchi Y, Ikuta M and others. The efficacy of self-administered stretching for finger joint motion in Japanese patients with systemic sclerosis. J Rheumatol 2006;33:1586-92.

[82] Bongi SM, Del Rosso A, Galluccio F, Sigismondi F, Miniati I, Conforti ML, Nacci F, Cerinic MM. Efficacy of connective tissue massage and Mc Mennell joint manipulation in the rehabilitative treatment of the hands in systemic sclerosis. Clin Rheumatol 2009;28:1167-73.

[83] Sandqvist G, Akesson A, Eklund M. Evaluation of paraffin bath treatment in patients with systemic sclerosis. Disabil Rehabil 2004;26:981-7.

[84] Poole JL, Watzlaf VJ, D'Amico F. A five-year followup of hand function and activities of daily living in systemic sclerosis (scleroderma). J Hand Ther 2004;17:407-11.

[85] Bostrom C, Harms-Ringdahl K, Nordemar R. Clinical reliability of shoulder function assessment in patients with rheumatoid arthritis. Scand J Rheumatol 1991;20:36-48.

[86] Bostrom C, Harms-Ringdahl K, Nordemar R. Shoulder, elbow and wrist movement impairment--predictors of disability in female patients with rheumatoid arthritis. Scand J Rehabil Med 1997;29:223-32.

[87] Csuka M, McCarty DJ. Simple method for measurement of lower extremity muscle strength. Am J Med 1985;78:77-81.

[88] Jones CJ, Rikli RE, Beam WC. A 30-s chair-stand test as a measure of lower body strength in community-residing older adults. Res Q Exerc Sport 1999;70:113-9.

[89] Collado-Mateo D, Dominguez-Munoz FJ, Adsuar JC, Merellano-Navarro E, Olivares PR, Gusi N. Reliability of the Timed Up and Go Test in Fibromyalgia. Rehabil Nurs 2018;43:35-9.

[90] Alexanderson H, Broman L, Tollback A, Josefson A, Lundberg IE, Stenstrom CH. Functional Index-2: Validity and reliability of a disease-specific measure of impairment in patients with polymyositis and dermatomyositis. Arthritis Rheum 2006;55:114-22.

[91] El-Baalbaki G, Lober J, Hudson M, Baron M, Thombs BD. Measuring pain in systemic sclerosis: comparison of the short-form McGill Pain Questionnaire versus a single-item measure of pain. J Rheumatol 2011;38:2581-7.

[92] Williamson A, Hoggart B. Pain: a review of three commonly used pain rating scales. J Clin Nurs 2005;14:798-804.

[93] Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol 1989;46:1121-3.

[94] Belza BL. Comparison of self-reported fatigue in rheumatoid arthritis and controls. J Rheumatol 1995;22:639-43.

[95] Steen VD, Medsger TA, Jr. The value of the Health Assessment Questionnaire and special patient-generated scales to demonstrate change in systemic sclerosis patients over time. Arthritis Rheum 1997;40:1984-91.

[96] Pope J. Measures of systemic sclerosis (scleroderma): Health Assessment Questionnaire (HAQ) and Scleroderma HAQ (SHAQ), physician- and patient-rated global assessments, Symptom Burden Index (SBI), University of California, Los Angeles, Scleroderma Clinical Trials Consortium Gastrointestinal Scale (UCLA SCTC GIT) 2.0, Baseline Dyspnea Index (BDI) and Transition Dyspnea Index (TDI) (Mahler's Index), Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR), and Raynaud's Condition Score (RCS). Arthritis Care Res (Hoboken) 2011;63 Suppl 11:S98-111.

[97] Devlin NJ, Brooks R. EQ-5D and the EuroQol Group: Past, Present and Future. Appl Health Econ Health Policy 2017;15:127-37.

[98] Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473-83.

[99] Swigris JJ, Esser D, Conoscenti CS, Brown KK. The psychometric properties of the St George's Respiratory Questionnaire (SGRQ) in patients with idiopathic pulmonary fibrosis: a literature review. Health Qual Life Outcomes 2014;12:124.

[100] Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. J Psychosom Res 2002;52:69-77.

[101] Hagstromer M, Ainsworth BE, Oja P, Sjostrom M. Comparison of a subjective and an objective measure of physical activity in a population sample. J Phys Act Health 2010;7:541-50.

[102] Bostrom C, Karreskog H, Eriksson K, Bergstrom M, Svenungsson E. Reliability and validity of a questionnaire assessing different aspects of physical activity in patients with systemic lupus erythematosus. Ann Rheum Dis 2011;70:776.

[103] Eriksson K, Svenungsson E, Karreskog H, Gunnarsson I, Gustafsson J, Moller S, Pettersson S, Bostrom C. Physical activity in patients with systemic lupus erythematosus and matched controls. Scand J Rheumatol 2012;41:290-7.

[104] Johnson SR, O'Brien KK. Qualitative Methods in Systemic Sclerosis Research. J Rheumatol 2016;43:1265-7.

[105] Saketkoo LA, Pauling JD. Qualitative Methods to Advance Care, Diagnosis, and Therapy in Rheumatic Diseases. Rheum Dis Clin North Am 2018;44:267-84.

[106] Vaismoradi M, Turunen H, Bondas T. Content analysis and thematic analysis: Implications for conducting a qualitative descriptive study. Nurs Health Sci 2013;15:398-405.

[107] Graneheim UH, Lundman B. Qualitative content analysis in nursing research: concepts, procedures and measures to achieve trustworthiness. Nurse Educ Today 2004;24:105-12.

[108] Moser A, Korstjens I. Series: Practical guidance to qualitative research. Part 3: Sampling, data collection and analysis. Eur J Gen Pract 2018;24:9-18.

[109] Landis JR, Koch GG. An application of hierarchical kappa-type statistics in the assessment of majority agreement among multiple observers. Biometrics 1977;33:363-74.

[110] Olofsson Y, Book C, Jacobsson LT. Shoulder joint involvement in patients with newly diagnosed rheumatoid arthritis. Prevalence and associations. Scand J Rheumatol 2003;32:25-32.

[111] Newcomer KL, Krug HE, Mahowald ML. Validity and reliability of the timed-stands test for patients with rheumatoid arthritis and other chronic diseases. J Rheumatol 1993;20:21-7.

[112] Sullivan M, Karlsson J, Taft C, Ware JE. SF-36 hälsoenkät : svensk manual och tolkningsguide = (Swedish manual and interpretation guide). Göteborg: Sahlgrenska sjukhuset, Sektionen för vårdforskning; 2002.

[113] Korstjens I, Moser A. Series: Practical guidance to qualitative research. Part 4: Trustworthiness and publishing. Eur J Gen Pract 2018;24:120-4.

[114] Johnson R, Waterfield J. Making words count: the value of qualitative research. Physiother Res Int 2004;9:121-31.

[115] Munro BH. Statistical methods for health care research. Philadelphia: Lippincott; 1997. 444 s. p.

[116] World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. Jama 2013;310:2191-4.

[117] Paterson BL. The shifting perspectives model of chronic illness. J Nurs Scholarsh 2001;33:21-6.

[118] Araujo A. COPD and physical activity. Rev Port Pneumol (2006) 2016;22:299-301.

[119] Levis B, Kwakkenbos L, Hudson M, Baron M, Thombs BD. The association of sociodemographic and objectively-assessed disease variables with fatigue in systemic sclerosis: an analysis of 785 Canadian Scleroderma Research Group Registry patients. Clin Rheumatol 2017;36:373-9.

[120] Justo AC, Guimaraes FS, Ferreira AS, Soares MS, Bunn PS, Lopes AJ. Muscle function in women with systemic sclerosis: Association with fatigue and general physical function. Clin Biomech (Bristol, Avon) 2017;47:33-9.

[121] Amici DR, Pinal-Fernandez I, Pagkatipunan R, Mears A, de Lorenzo R, Tiniakou E, Albayda J, Paik JJ, Lloyd TE, Christopher-Stine L and others. Muscle endurance deficits in myositis patients despite normal manual muscle testing scores. Muscle Nerve 2019;59:70-5.

[122] Alexanderson H, Regardt M, Ottosson C, Alemo Munters L, Dastmalchi M, Dani L, Lundberg IE. Muscle Strength and Muscle Endurance During the First Year of Treatment of Polymyositis and Dermatomyositis: A Prospective Study. J Rheumatol 2018.

[123] Panagiotou M, Polychronopoulos V, Strange C. Respiratory and lower limb muscle function in interstitial lung disease. Chron Respir Dis 2016;13:162-72.

[124] Mendes P, Wickerson L, Helm D, Janaudis-Ferreira T, Brooks D, Singer LG, Mathur S. Skeletal muscle atrophy in advanced interstitial lung disease. Respirology 2015;20:953-9.

[125] Hudson M, Thombs BD, Steele R, Panopalis P, Newton E, Baron M. Quality of life in patients with systemic sclerosis compared to the general population and patients with other chronic conditions. J Rheumatol 2009;36:768-72.

[126] Chung L, Chen H, Khanna D, Steen VD. Dyspnea assessment and pulmonary hypertension in patients with systemic sclerosis: utility of the University of California, San Diego, Shortness of Breath Questionnaire. Arthritis Care Res (Hoboken) 2013;65:454-63.

[127] Baron M, Sutton E, Hudson M, Thombs B, Markland J, Pope J, Robinson D, Jones N, Docherty P, Abu-Hakima M and others. The relationship of dyspnoea to function and quality of life in systemic sclerosis. Ann Rheum Dis 2008;67:644-50.

[128] Joachim G, Acorn S. Life with a rare chronic disease: the scleroderma experience. J Adv Nurs 2003;42:598-606.

[129] Ainsworth B, Levy S. Assessment of health-enhancing physical activity. Methodological issues. In: Health Enhancing Physical Activity, P. Oja and J. Borms (Eds.). Oxford, UK: Meyer & Meyer Sport. 2004:239-70.

[130] Jette M, Sidney K, Blumchen G. Metabolic equivalents (METS) in exercise testing, exercise prescription, and evaluation of functional capacity. Clin Cardiol 1990;13:555-65.

[131] Hagstromer M, Oja P, Sjostrom M. Physical activity and inactivity in an adult population assessed by accelerometry. Med Sci Sports Exerc 2007;39:1502-8.

[132] Gumuchian ST, Pelaez S, Delisle VC, Carrier ME, Jewett LR, El-Baalbaki G, Fortune C, Hudson M, Korner A, Kwakkenbos L and others. Understanding coping strategies among people living with scleroderma: a focus group study. Disabil Rehabil 2018;40:3012-21.

[133] Mouthon L, Alami S, Boisard AS, Chaigne B, Hachulla E, Poiraudeau S. Patients' views and needs about systemic sclerosis and its management: a qualitative interview study. BMC Musculoskelet Disord 2017;18:230.

[134] Pauling JD, Domsic RT, Saketkoo LA, Almeida C, Withey J, Jay H, Frech TM, Ingegnoli F, Dures E, Robson J and others. Multinational Qualitative Research Study Exploring the Patient Experience of Raynaud's Phenomenon in Systemic Sclerosis. Arthritis Care Res (Hoboken) 2018;70:1373-84.

[135] Morgan DL. Focus groups as qualitative research [Elektronisk resurs]. Thousand Oaks, Calif.: SAGE; 1997.

[136] World Health Organization. Switzerland: World Health Organization; 2010 -]; Available from: http://apps.who.int/iris/bitstream/10665/44399/1/9789241599979_eng.pdf.

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